

Medication Guide Comprehension and Health Literacy

BY

JAMES E. DUHIG

B.A., University of Illinois at Urbana-Champaign, 2001

M.A., University of Illinois at Chicago, 2006

THESIS

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Defense Committee

Bruce L. Lambert, Chair and Advisor
Stephanie Crawford
Nicholas Popovich
William Galanter, College of Medicine
Michael Wolf, Northwestern University

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JED

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LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
AHRQ	Agency for Healthcare Research and Quality
DDMAC	Division of Drug Marketing, Advertising, and Communications
EMA	European Medicines Agency
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
FDAAA 2007	Food and Drug Administration Amendments Act of 2007
HCP	Health Care Provider
IOM	Institute of Medicine
IRB	Institutional Review Board
Med Guides	Medication Guides
MMSE	Mini-Mental State Examination
NAAL	National Assessment of Adult Literacy
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital and Ambulatory Care Survey
NME	New Molecular Entity
PI	Prescribing Information
PPI	Patient Package Inserts
RA	Research Assistant
REALM	Rapid Estimate of Adult Literacy in Medicine
REMS	Risk Evaluation and Mitigation Strategies
SIS	Six-Item Screener

LIST OF ABBREVIATIONS (continued)

TNF blockers Tumor Necrosis Factor-Alpha Blockers

WHO World Health Organization

SUMMARY

Written information is often distributed with prescription medications in order to help patients understand, anticipate, and manage risks. Several factors, most significantly a low level of health literacy, prevent patients from fully comprehending this information. Particularly disturbing is that for drugs requiring medication guides, there are well-established risks that patients need to understand. Patients are often unable to identify these risks and therefore unable to participate actively in risk management. This study investigated the relationships among health literacy, functional tests of patient comprehension, and the usefulness of medication guides.

Four hundred forty-nine patients were assessed at two separate urban academic medical centers. Patients' comprehension of a selection of medication guides was captured during patient interviews along with their demonstrated health literacy level.

The study's results demonstrated patients' inability to comprehend the risk information in medication guides. Patients with lower literacy were significantly less able to navigate and retrieve information and to make inferences to support the safe and appropriate use of a medicine. Not surprisingly given the degree of difficulty of these medication guides and the strong associations with literacy skills, less education was also independently linked to poorer functional comprehension. In comparison to set standards for warning and risk communication, patients did not comprehend a high enough percentage of content contained in medication guides for those guides to act as an effective risk information or risk mitigation tool.

These findings, when considering other failed sources of written drug information and prescription labeling that have been identified in previous research, represent a call-to-action to apply evidence-based, health literacy principles to the redesign of the medication guide program.

1. INTRODUCTION

Patients' inability to correctly use prescribed medications is a major source of patient harm leading to injury, hospitalization, and death. Medication guides (med guides) are a consumer-directed tool approved by the Food and Drug Administration (FDA) to increase patient understanding and utilization of medicines.¹⁻³ When the FDA determines that providing the patient with specific information is essential to the product's successful use, then a med guide must be dispensed with that particular prescription drug or biologic product.^{3,4} The usefulness of med guides in improving patient understanding of drug products' benefits and risks is an area of considerable debate. Medication guides provide the patient with a paper copy of drug product information reviewed by the FDA in accordance with set standards on content, format, and distribution requirements.² Despite these standards, available evidence combined with decades of experience fuels consensus that med guides function poorly as a patient information tool.⁵⁻⁹ From the FDA, health care providers (HCPs), academic researchers, and the pharmaceutical industry there is strong support for the need to move to a more effective method of written drug risk/benefit information to patients.⁵⁻¹¹ Multiple government reports—most notably the Keystone Dialogue in 1996—and presentations to the FDA concur on the general deficiency of med guides.^{12,13} A large body of anecdotal evidence from HCPs supports the position that med guides are too complicated for most patients to understand.^{5,14} At the time of this study there was little empirical evidence investigating patients' abilities to process and understand content in existing med guides. Understanding precisely where, why, and how med guides do and do not work is of increased importance for patients with limited health literacy skills. This group numbers 90 million persons in the United States.¹⁵⁻¹⁷ The move to a more effective method of risk communication needs to be rooted in a firm understanding of the insufficiencies of the old

method. If new patient information tools are to be created, there first needs to be an accurate understanding of how current med guides fail to meet the needs of patients and providers.

1.1 Research Question

The research question for this dissertation asked, How well do patients with varying levels of health literacy comprehend information contained in current medication guides? Given their required use in over 295 drug and biologic products in the U.S., there has been a surprising lack of research that directly assesses patient capacity to understand med guide content.¹¹ Previous investigations described reasons why med guides were likely not to be useful to patients, but there were few instances of first-hand patient testing of med guide content comprehension that included a measure of the patient's health literacy.^{11, 16, 18-22}

1.2 Objective

The study objective was to assess patients' ability to process and correctly understand existing med guide content. Patient ability to review a selection of current med guides and then demonstrate comprehension of key areas of content—including indication, directions for use, risks, warnings, side effects, storage, and other general information—was examined. Patient performance was considered with respect to ascertained level of health literacy, age, and other demographic characteristics.

1.3 Hypotheses

The research question led to the two hypotheses examined in this study. Each will be discussed after it is presented.

- H1: Patients will comprehend less than 80% of the content contained in med guides. First, patients will make mistakes in understanding med guide content. The rate these mistakes occur will indicate understanding of med guides is not adequate to inform patients' decision-making process. Although guidelines for adequate understanding of drug product information had not been established by the FDA, the European Medicines Agency (EMA), through the European Commission on

Enterprise and Industry Directorate–Consumer Goods, Pharmaceuticals, had determined success criteria for patient understanding of drug product information. The EMEA standards stated that patient understanding of drug product information is successful when patients are able to demonstrate comprehension at a rate of 80% or greater when assessed.²³ The methods for the EMEA standard assessment were highly consistent with the methods used in the current study. Therefore, the performance standard of 80% or greater patient comprehension was used to determine successful comprehension from inadequate comprehension.

The primary outcome measure of this study was patient comprehension. Patient comprehension was defined as the patient's functional capacity to read or identify and then process information consistent with the underlying concept of the information source.^{14, 24-26} In practical terms, patient comprehension means that the patient is capable of identifying the risks of the drug, identifying the benefits of the drug, and then weighing the significance of the risks against the significance of the benefits in the context of his or her personal experience. Patient comprehension was used throughout this research consistent with the term patient functional comprehension. Functional comprehension is a refinement of the idea of comprehension as a dichotomous outcome (patient comprehends: yes or no) into a more layered concept with degrees of patient understanding.²⁶ Patient comprehension's measurement operationalization will be explained in greater detail in section 2.5.1.

Because this was one of the first investigations to directly test patient comprehension of med guides, it was not possible to set an error rate that translated into an increased likelihood of clinical harm. The results of this investigation contribute to establishing a baseline rate of patient error in med guide comprehension. This project provided an initial step toward that goal.

H2: Patient comprehension of med guide content is associated with health literacy, with low levels of health literacy predicting low levels of patient comprehension.

Additionally, patient ability to read and understand med guides will correlate to demonstrated level of health literacy. This means that patients with low health literacy will demonstrate low

levels of comprehension, and patients with high levels of health literacy will score high on comprehension. This relationship is important because for any given product there is only one version of the med guide distributed. Regardless of the reason for the prescription, the patient's experience, education, or cognitive status, all patients receive the same med guide. (For instance, a 30-year-old lawyer prescribed a biologic product for Crohn's disease receives the same med guide as a 74-year-old retired cashier prescribed the same biologic product for rheumatoid arthritis.) Multiple factors affect patient ability to read and understand the med guide. Based on prior research, health literacy is likely the most significant factor predicting patient understanding.^{11, 27-31} This study was one of the first to assess the relationship between med guide comprehension and health literacy.

1.4 Significance

The 2006 Institute of Medicine (IOM) report, *Preventing Medication Errors*, conservatively estimated there were at least 1.5 million preventable adverse drug events (ADEs) in the United States each year.³² Over one third of these events occurred in outpatient settings at an annual cost nearing \$1 billion.³² The challenges facing patient safety efforts to reduce medication errors were predicted to become more difficult as more patients took more drugs. This would happen as the U.S. population shifted with the aging of the baby boom cohort and there was an increased reliance on pharmaceutical care resulting from growth in chronic disease conditions, availability of drug options, and decreased patient-provider time interaction, among other factors.⁸ Additionally, ambulatory patients have become increasingly responsible for using their prescribed medications correctly.³³ However, tens of millions of patients were estimated to have impaired health literacy, with IOM using Ratzan and Parker's 2000 definition, "Health literacy is the degree to which individuals have the capacity to obtain, process, and understand

basic health information and services as necessary to make appropriate health decisions” (p. 183).¹⁷ These factors combine to form a situation where patients have tremendous need for materials to assist them in correctly using their medications.

1.5 Overview

This study investigated the relationships among health literacy, functional tests of patient comprehension, and the usefulness of medication guides. Chapter 2 explains the rationale of this research through the relationships among medication errors, health literacy, and the necessity of well-functioning risk communication tools in the provision of care. Chapter 2 further specifies the measurement of patient comprehension and provides a conceptual framework for analyzing these relationships. Chapter 3 describes the methods, including the research design, protocol, and statistical analyses. Chapter 4 provides the research results. Chapter 5 discusses the implications of the results, the study’s limitations, and recommends future research on med guides.

2. BACKGROUND, RATIONALE, LITERATURE REVIEW, SIGNIFICANCE OF STUDY

Following the start of the Institute of Medicine's *Quality Chasm Series* of reports, patient safety efforts gained substantial research prominence and momentum throughout the practice of health care.³⁴ The IOM defined patient safety as "the prevention of harm to patients" (p. 5), but a more functional definition comes from the Agency for Healthcare Research and Quality (AHRQ) Patient Safety Network: "freedom from accidental or preventable injuries produced by medical care" ("Glossary: Patient Safety").^{35, 36} The concept at the heart of patient safety is that medical care commonly produces unintended consequences that hurt patients and that the provision of care can be improved to reduce harm.

This chapter explores the connection between medication errors and med guides. Section 2.1 explores medication errors' increasing threat to patient safety. Section 2.2 introduces risk communication and its function in health care. Section 2.3 reviews the history of med guides as a risk communication tool. Section 2.4 focuses on the impact of health literacy. Section 2.5 includes the operationalization of patient comprehension as an outcome measure and provides the conceptual framework for this research. Lastly, Section 2.6 outlines the value of med guide research.

2.1 Medication Errors

Medication errors are a substantial patient safety concern for HCPs and patients. The frequency of medication errors is the most compelling reason for investigating med guides, with over a million and a half instances of harm in the U.S. each year.³⁶ Moreover, these medication errors are classified as preventable adverse drug events (ADEs). A medication error is defined as any error occurring in the medication-use process.³⁷ An ADE is any injury due to medication.³⁸

The two definitions formulate a preventable ADE as any ADE arising because of an error.³⁶

Preventable ADEs and their estimated billion dollar annual cost to the health care system are a significant threat to patients in hospitals and in outpatient care.³⁶

The quality of pharmacologic care in the U.S. displays systematic deficiencies in every dimension of prescribing quality: overuse, underuse, documentation, monitoring, and education.³⁹ Prescribing quality is more than a lack of monetary resources to provide appropriate drug therapy. A study comparing quality of prescribing to quantity spent on therapeutics demonstrated wide geographic variation throughout the country, where areas of higher spending were only sporadically correlated with areas of improved prescribing quality.⁴⁰ The endemic nature of medication errors is partly derived from this persistent pattern of suboptimal prescribing. Suboptimal prescribing practices contribute to making medication errors a significant source of patient harm in all health care settings, for all patients.

Two thirds of all preventable adverse events are medication related.⁴¹ It is most common for medication errors to be investigated in hospital settings.^{34, 36} In a hospital setting, the stages of the drug usage process—prescribing, transcribing, dispensing, administering, monitoring, and patient education—are largely under the direct control of HCPs. This facilitates research by providing more control in the experimental environment, making inpatient studies of medication errors less likely to contain spurious factors. However, these studies to a large extent exclude patient behavior because the patient is essentially a passive actor simply consuming the medication. Ambulatory patients are actively involved in their own medication decision-making. In ambulatory care the patient is primarily responsible for administering his or her medication appropriately and monitoring him- or herself for adverse effects. The safety burden shifts to the patient from the HCP.⁴² Whereas the role of the HCP and the health care system are regularly

investigated for contributions to medication errors, with retail pharmacies in the U.S. filling over 3.6 billion prescriptions in 2009, ambulatory medication errors are an underdeveloped area of research.^{43, 44}

Investigating medication errors in ambulatory patients presents numerous challenges. The current literature on ambulatory patient medication errors varies widely in terms of error frequency. Annual ADE proportion estimates for outpatients range from 5% to 35%.^{45, 46} Much of the existing ADE research in outpatients consists of drug trials.³³ But the degree of control and patient selection for drug trials make these dissimilar to the average ambulatory patient experience, limiting the generalizability of their results. Emergency department visits for ADEs are one indicator of medication harm for the outpatient population. A 2006 national survey estimated that annually more than 700,000 patients are treated for an ADE in emergency departments in the U.S.⁴⁷ These events account for 2.5% of all emergency department visits for unintentional injuries.⁴⁷

Moreover, the rate at which medication errors occur in outpatients is increasing. An analysis of the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital and Ambulatory Care Survey (NHAMCS) from 1995 to 2005 demonstrated a substantial increase in the incidence of ADEs requiring medical treatment from outpatient clinics.⁴⁸ In a comparison of the rate of ADE visits to outpatient clinics for the years 1995-2000 versus 2001-2005 the mean ADE visit incidence rose from 13.2 events per 1,000 persons to 18.1 events per 1,000 persons, respectively.⁴⁸ The rate of outpatient clinic visits due to an ADE grew even faster, to an incidence approaching 1 out of every 20 persons for patients 65 years and older.⁴⁸

Several trends suggest explanations why medication errors are increasing. First, the U.S. population is on average growing older with the aging of the baby boom cohort.⁴³ In 2011, the

first baby boomers are reaching the age of 65. Persons over 65 fill almost three times as many prescriptions in ambulatory pharmacies versus persons aged 19 to 64.^{43, 48} More people will consume more drugs as this population bubble continues to grow older. Additionally, the elderly demonstrate increased vulnerability to adverse drug events due to impaired cognition and vision with aging.³⁶

Medication error rates are also increasing because of limits on patient-provider interaction resulting from pressures of managed care systems. The average time spent with a patient by a HCP markedly decreased over the past 20 years.^{34, 36} Health care providers' spending less time with patients combined with the increasing complexity of pharmacotherapy form a situation where the demands placed upon patients to administer and monitor their own care frequently outweigh patients' capabilities.^{8, 21}

2.2 Risk Communication

A major strategy to reduce medication errors is to improve the communication of a medication's risks. Communicating the risks of medications is a practice that dates back to antiquity. The original Greek term for drug, *pharmakon*, conveyed three meanings: remedy, magical charm, and poison.⁴⁹ Recognition of the dangers associated with medications is a socially constructed artifact.⁵⁰ The meaning ascribed to taking medications depends on cultural conventions and personal experiences that shape patients' attitudes and decision-making.⁵¹ Patients take bits and pieces of knowledge from all different sources and combine them to form an understanding of what the medication "does." These include patients' understanding of information from the HCP, previous personal experience, the experience of friends and relatives, a medication's advertising, news items, and information patients search for independently, most commonly via the Internet. The intent of risk communication is that, in conjunction with all the

other information patients receive regarding a medication, patients also be informed of the possible negative outcomes.

Risk communication is a subset of the larger discipline of risk management. The definitions for risk management and risk communication are highly specific to context; both of these terms are used to describe structures and processes in a variety of disciplines and fields.^{26, 52-56} Specific to medications, the FDA provides the most germane definition of risk management as the continual process of monitoring and evaluating drug products and outcomes to identify possible sources of harm and opportunities for improving.⁵² Risk management breaks down into the activities of risk assessment, the estimation and evaluation of risk; risk confrontation, determining acceptable level of risk in a larger context; risk intervention, controlling risk actions; risk communication, the interactive process of exchanging risk information; and risk management evaluation, measuring and ensuring the effectiveness of risk management efforts.⁵² By FDA regulatory authority, risk information includes a drug product's risks, warnings, contraindications, side effects, cautions, and any special considerations for the drug's use.^{57, 58}

Since the start of the twentieth century, risk communication in the U.S has revolved around the regulatory authority of the FDA. The seminal 1906 Pure Food and Drugs Act charged the FDA (then known as the Bureau of Chemistry) with the responsibility of ensuring drug product information was not misbranded.^{59, 60} As drug safety developments coincided with drug disasters through the years, the FDA continually initiated and refined methods of communicating drug risks.^{2, 12, 52, 60} Consistent with its original mission to ensure the drug product box contained no false claims, the main area of concentration for the FDA's risk communication programs is product labeling. Product labeling is a composite term used by the FDA to encompass any text,

images/graphics, or packaging included with the drug product. This includes written information provided to the patient. Written patient information is classified into these categories:

- Drug product container labeling
- In-package Prescribing Information, commonly abbreviated PI
- Patient Package Inserts (PPI)
- Consumer Medication Information⁶¹
- Medication Guides (med guides)^{2, 3, 25, 57, 62, 63}

Past research demonstrates patient difficulties in comprehending risk from all of these sources of written patient information.

Prescribing information on the package insert is commonly referred to as the drug's PI. It is the FDA-approved labeling text that summarizes much of the product knowledge. Typically, the PI includes a summary of the main clinical studies the FDA reviewed prior to approval for sale in the U.S.⁵⁸ By law, a PI is required to accompany each individual unit of shipped drug product. The PI is also referred to as the drug product's label. The PI is considered the first line of risk communication. All marketing efforts by a drug manufacturer must be "label consistent" or the drug may found to be misbranded.⁵⁹ This sets up a situation where the PI is essentially the negotiated battleground between the manufacturers' marketing efforts versus risk disclosure efforts by the FDA as regulator. From the regulator's perspective, it is essential that the requisite risk information be disclosed in manner most likely to prevent harm and improve outcomes. For the manufacturer, the focus changes because of its financial concern, marketplace competition, and, interestingly, the nature of risk communication for products considered 'safe.'

A basic marketing principle is to highlight a product's benefits to the consumer and minimize its negatives.⁶⁴ Specific to pharmaceuticals, this means maximize the benefits, minimize the risks. The marketplace further depresses manufacturer willingness to disclose risk

information because risks identified in the product's PI are used by competitors as fuel for their own product's superiority. There are many instances where drugs in the same class, with the same indication, and similar pharmacology, will have different risks disclosed in the PI. The PI is approved by the FDA but produced by the manufacturer, so the text of the PI becomes a product of negotiation when the drug is approved and throughout its sales life. Any changes due to safety concerns or new information may be mandated by the FDA, commonly referred to as 'label changes,' but manufacturers often appeal changes to the label. These appeals require time for the manufacturer and the FDA to reach consensus. Also, the FDA must allow time for the manufacturer to change the thousands, and in some cases millions, of PIs attached to each unit of sale. What results is a great deal of 'gamesmanship' on manufacturer's part to phrase drug risks in as favorable terms as possible from the outset and to resist any changes due to safety information.

Warning and risk communication research indicates drug products are particularly sensitive to negative perceptions, resulting in decreased sales from explicit risk disclosures, because drugs are assumed to be a 'safe' versus a 'dangerous' product.²⁶ For products that are generally considered dangerous or harmful, risk disclosures through warnings or labeling can actually improve perceptions of the products' safety. For example, for a product like a chain saw, the danger associated with its use is clearly evident. A more detailed description of how the saw may malfunction or specific situations where the user would place him- or herself at greater than normal operational risk actually improves perception of the saw's safety. Written information that the saw should not be used in temperatures below a certain point or above a certain point increases consumer confidence in correct operation. But drugs are widely perceived as a safe product and the opposite effect holds true. The greater the amount of risk disclosed about a 'safe'

product, the more likely the information will produce a negative viewpoint of the drug in the mind of the consumer because the risk information is subtracting from his or her positive starting point of perception.

2.3 Medication Guides

Medication guides are a consumer-directed tool approved by the FDA to increase patient understanding and the utility of medicines.¹⁻³ Starting in practice in 1993 and formalized into law in 1998, when the FDA determined that providing the patient with specific information was essential to the product's successful use, a med guide was required to accompany a prescription drug or biologic product.^{3, 57} The FDA specifies three criteria for requiring a med guide:

- Certain information is necessary to prevent serious adverse effects
- Patient decision-making should be informed by information about a known serious side effect with a product
- Patient adherence to directions for the use of a product are essential to its effectiveness⁵⁷

Medication guides are an exception to most written patient information in that there exist clearly defined standards for included content.^{2, 3, 11, 58} However, despite federally regulated standards, there still exist wide discrepancies in how med guide are written.^{9, 11}

Moreover, the number of med guides for new drugs and existing drugs increased dramatically in the past five years. In 2006, the FDA required med guides for licensed sales of 40 separate drug products. By June 2011 that number increased to 295 different drug products that required a med guide.⁴ From January 1, 2011, to June 1, 2011, the FDA approved 14 drugs categorized as new molecular entities (NMEs), essentially a new drug or biologic compounds.⁵⁷ During that same time period, the number of new or existing drug products requiring med guides increased by 35.

2.3.1 Risk Evaluation and Mitigation Strategies

A major reason for this increase was the Food and Drug Administration Amendments Act of 2007 (FDAAA 2007).⁶³ This act augmented the regulatory authority of the FDA in numerous ways. Particular to med guides, FDAAA 2007 clearly defined the FDA's authority to require a risk management program for both newly approved drug products and drug products already in the market.⁶³ The Risk Evaluation and Mitigation Strategies (REMS) program was designed to improve risk communication and lessen the opportunity, severity, and impact of medication errors.⁶⁵ Medication guides are one of the essential elements of the REMS program.

The REMS program is remarkable because it represents the first major risk communication program other than the product label that grants the FDA regulatory authority through Congressional legislation.^{63, 65, 66} This is a critical distinction from the FDA's prior drug safety programs. Drug safety programs often require increased pharmacovigilance efforts from manufacturers that typically translate into increased costs and may threaten marketing efforts.⁶⁷ Pharmaceutical manufacturers historically use legal challenges to limit the impact of these programs.⁶⁷ For example, FDA guidelines mandate the inclusion of essential content and specify the format of direct-to-consumer advertisements of prescription drug products. Through the Division of Drug Marketing, Advertising, and Communications (DDMAC), drug ads are reviewed for accuracy of claims, inclusion of risk information, and fair balance between benefits and risks depicted. The DDMAC's authority to make such decisions is frequently challenged in federal courts as infringement upon freedom of speech.⁶⁸ These challenges come from pharmaceutical industry political advocacy and lobbying groups, such as the Washington Legal Foundation. Even when their authority is upheld, DDMAC activities are limited from these challenges to highly specific actions. The result is a situation where DDMAC guidelines contain

a large number of exact behaviors that are deemed violations.⁶⁹ In other words, because of the lack of statutes on regulating advertising, manufacturers fall into the pattern of following only the letter of the law versus the intent. Consequently, the DDMAC must police activity, indict violators with a warning letter, and then defend its right to do so in federal court. Conversely, REMS has detailed statutory authority, granting the FDA particular powers of enforcement.⁶⁶ This places the onus on manufacturers to comply with the REMS guidelines or face definite penalties.

The FDAAA 2007 requires a REMS program when necessary to ensure the benefits outweigh the risks of allowing a drug on the market. The FDA lists specific criteria it uses in making this determination in the REMS Draft Guidance from September 2009.⁷⁰ The criteria are the following:

- Size of the population likely to use the drug
- Seriousness of the disease or condition the drug is used to prevent, treat, or ameliorate
- Expected benefits of the drug
- Duration of expected use of the drug
- Seriousness of any/all specific known risks associated with the drug or drug class
- Whether the drug is a new molecular entity
- Potential of the drug to be misused

On a practical level the concept behind REMS is to allow access to drugs for which the normal safety information—the approved labeling—is likely insufficient. Risk Evaluation and Mitigation Strategies consist of multiple components of risk communication. The components of REMS include med guides to patients, communication plans to HCPs, specific usage or monitoring programs, called elements, to assure safe use (ETASUs), assessments of the REMS program by the manufacturer, and a timetable of those assessments.⁷⁰ Not all of these

components are required in each individual drug product's REMS. Medication guides are the first REMS element and by far the most common. The 177 drug products with REMS include 16 drugs that were on the REMS precursor program, called RiskMaps. Of those 177 REMS, 111 (63%) include a med guide only.

The FDA employs the REMS elements of med guides, HCP communication plans, and ETASUs in a hierarchical manner.⁷¹ Medication guides are the first level of increased risk communication to inform the patient. The next step up is HCP communication plans, which are used to inform health professionals of drug risks where the complexity of the risk requires HCP expertise to understand the potential impact on the patient.⁷² For example, biologic agents referred to as tumor necrosis factor-alpha blockers (TNF blockers) pose an increased risk of invasive fungal infections.⁷³ In certain geographic areas of the U.S., such as the Ohio River Valley, the fungal infection histoplasmosis is much more likely to occur and patients on TNF blockers are at increased risk. To address this complex risk as a class, TNF blockers are all mandated to include a REMS program that distributes a med guide to patients and also provides a 'Dear Healthcare Professional' letter to HCPs, detailing the risk.⁷¹ The REMS that include a med guide and a HCP communication plan are about 21% (38 of 177) of the total number of REMS programs.

More rarely, ETASUs are required. Typically, these are associated with an explicit identified safety concern and call for patient and/or provider action plans and perhaps the use of a specialized pharmacy to mitigate risk.⁷² The iPledge for accutane is an example of an ETASU program. Before receiving accutane, patients must complete an education program that emphasizes the teratogenic nature of accutane. Also, if female, the HCP must certify the patient is not pregnant at the time of prescribing. Additionally, female patients must consent to the

continued use of one primary and one secondary form of birth control for the duration of their accutane use; HCPs are responsible to certify the patient has access to a primary form of birth control. The REMS that include an ETASU plan are about 14% (24 of 177) of the total number of REMS programs.⁷⁴ Finally, each REMS drug sponsor must provide assessments at 18, 36, and 72 months of the REMS functional results.⁷⁰ The FDA may adjust those time points.

The FDA can enforce noncompliance with REMS with fines of up to \$1 million per instance and it can remove the drug from market.⁶³ For manufacturers, REMS are a challenge because the activity cuts across multiple functions and requires a degree of coordination not commonly found in the silo structure of pharmaceutical companies. Additionally, the specifications of the program are continually changing. The initial draft guidance on REMS was released in 9/09; however, instead of moving towards final guidance, the FDA reopened the public commentary period. This was the first time the FDA ever reopened a public commentary period. Because FDAAA 2007 gives only 120 days for companies to comply with changes, this is a major challenge. The greatest advantage for companies is the opportunity to market drugs that might otherwise not be eligible for approval because of safety concerns. However, there is little support that REMS are in reality being applied in this manner; the general sentiment is that REMS are required for drugs that would have made it to market regardless but now have an added safety program burden.

2.3.2 Medication Guide Challenges

Directions for using drugs correctly are complicated.^{17, 19, 25, 75} Medication guides are designed to help patients make sense of a drug's complicated warnings, precautions, and instructions for use so that they can use the drug safely and enjoy the maximum benefit with the minimum risk.^{3, 11} Medication guides are one of numerous risk aversion tools and strategies

employed by HCPs and other stakeholders to improve the likelihood of a beneficial outcome from drug therapy.⁷⁶ The fundamental problem in constructing a med guide is how to take complicated information and write it in a way that can be understood best by the patient. The research, reports, and editorials on medication guides list ways to accomplish this task: make the information simpler, make it patient-friendly, use common language/avoid jargon, write the med guide to the 5th grade reading level, focus on the critical content, use figures, use block format or bolding or underlining, avoid circumstances where patients must perform computation, etc.^{8, 17, 19, 25, 76-78} These ideas all have some degree of merit. But the basic principle of med guides is to make technical information useful to a non-expert audience. This is a challenging task.

2.4 **Health Literacy**

Among the reasons med guides do not function well in explaining risk to patients is the low level of health literacy throughout the U.S. adult population. Health literacy is a significant barrier to patient safety efforts, in particular the utility of med guides. In the *Quality Chasm Series*, the IOM summarizes much of the available research in *Health Literacy: A Prescription to End Confusion*.¹⁷ While this is the most complete report to date of health literacy as a public health problem, a more accurate definition of health literacy comes from the World Health Organization (WHO).⁴⁰ The WHO defines health literacy as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good *health*” (italics in original; p. 10).⁷⁹ The WHO definition of health literacy is more complete because it is consistent with how the WHO defines health in considering the social, political, and environmental factors that determine health literacy and not just the absence of disease or harm.⁷⁹ Health literacy is more than information

absorption. Health literacy entails interaction, participation, and critical analysis. Health literacy is illustrated at the intersection of multiple conceptual domains, including the following:

- Health Knowledge
- Health Problem-solving
- Health Communication
- Health Beliefs
- Health Activation
- Health Behaviors
- Health System Awareness^{30, 31, 80}

The IOM report *A Prescription to End Confusion* identified a staggering fact—an estimated one third to one half of adults in the U.S. have limited health literacy skills.¹⁷ As many as 93 million Americans may have trouble engaging, understanding, and utilizing written medication information.¹⁶ Adult literacy in the U.S. was measured in 2003 by the National Assessment of Adult Literacy (NAAL). The NAAL 2003 assessed persons according to their performance on three literacy scales: prose literacy, document literacy, and quantitative literacy. The results classify persons into levels of below basic, basic, intermediate, and proficient.¹⁶ Fourteen percent of U.S. adults fall into the below basic level due to their prose and document literacy skills; this increases to 22% when determining quantitative literacy. Persons in the below basic level are able to perform only the simplest tasks with easily identifiable information. Moving to persons at the basic level increases domain literacy capacity to include reading and understanding of information only in short, simple documents and common texts and clearly defined arithmetic. Together, below basic and basic persons equal as many as 34% to 55% of the U.S. adult population.

Moreover, the literacy domains examined in NAAL 2003 generally consisted of a ‘plain language’ vocabulary. Written patient information, in particular med guides, makes use of specialized medical terminology that is unfamiliar to many individuals. In the NAAL 2003 there was a separate health literacy assessment to examine the effect of unfamiliar terms and content on literacy skills. The report showed a significant decrease in U.S. adult scores on health literacy versus general literacy.¹⁶ Written patient information is often composed at a reading level much more advanced than the skills of the intended audience.¹⁴ Medication guides in particular exceed the reading skills of the average high school graduate.¹⁷ Low literate patients may be confused and unable to comprehend the essential risk information med guides are required by federal law to provide.

The elderly are especially vulnerable to medication errors. More limited health literacy than the general population is one of several contributing factors. The elderly are also more likely to have cognitive and vision impairments that further impede literacy skills.^{30, 81, 82}

Medication guide comprehension prioritizes numeracy skills. Numeracy is an aspect of health literacy that refers to the ability to understand numbers.⁸³ Numeracy is especially relevant in med guides because risks and benefits may be expressed numerically as percentages or ratios. Also, statistical information is problematic because of the strong likelihood of patient misinterpretation.⁸⁴ Limited numeracy skills negatively affect patient ability to weigh long-term versus short-term benefits.⁸³ Finally, computation that includes multiple steps is difficult for most persons and likely to produce errors.^{17, 84-86}

2.5 Conceptual Framework—Patient Comprehension and the Information Processing Model

Understanding med guide functionality requires an understanding of how patients process information. First this section clarifies the project's main outcome measure, patient comprehension. Then this section outlines why the information processing model is the appropriate research paradigm to analyze patient comprehension's relationship to med guides and health literacy.

2.5.1 Patient Comprehension

Patient comprehension is a composite outcome measurement consisting of multiple assessed factors. Though patient comprehension studies are numerous, there is a lack of consistency in how comprehension was operationalized;^{9, 87, 88} measuring comprehension is highly specific to the format of the information assessed and the experimental time frame used.⁸⁹ The result is that comparisons among patient comprehension studies are difficult. As stated in Section 1.5, the format of this dissertation was consistent with the format mandated by the EMEA for patient comprehensibility studies of patient prescribing information conducted by drug manufacturers for licensed product sale in the EU.²³ The format used is med guides as unaccompanied text.

The experimental time frame used was purposefully limited to focus on the patients' use of short-term memory.²³ Short-term memory is desirable because long-term memory acts as a confounder in measuring comprehension;⁸⁹ the high degree of correlation between long-term memory and comprehension presents a problem of collinearity of measurement.⁸⁹ Restricting the amount of time from the introduction of the information to the start of the assessment limits the degree to which memory is measured versus comprehension.⁹⁰ Additionally, both memory and

comprehension of new information are heavily influenced by prior knowledge.²⁶ Prior knowledge provides a cognitive schema into which new information may be included. The more detailed the existing cognitive schema, the quicker and easier relevant new information may be absorbed and stored in long-term memory.²⁶ The implication is that as time from introduction of the information increases, it becomes more difficult to separate the measurement of comprehension from prior knowledge.

The critical element in operationalizing patient comprehension is that comprehension is a process of understanding the meaning of a concept as it connects to the whole message.⁹⁰ This process is broken down into specific steps to define what patient comprehension means in terms of actual abilities demonstrated by the patient.

Patient comprehension encompasses two domains: the ability to recognize a concept and the ability to understand a concept. Figure 1 depicts patient comprehension's functional domains

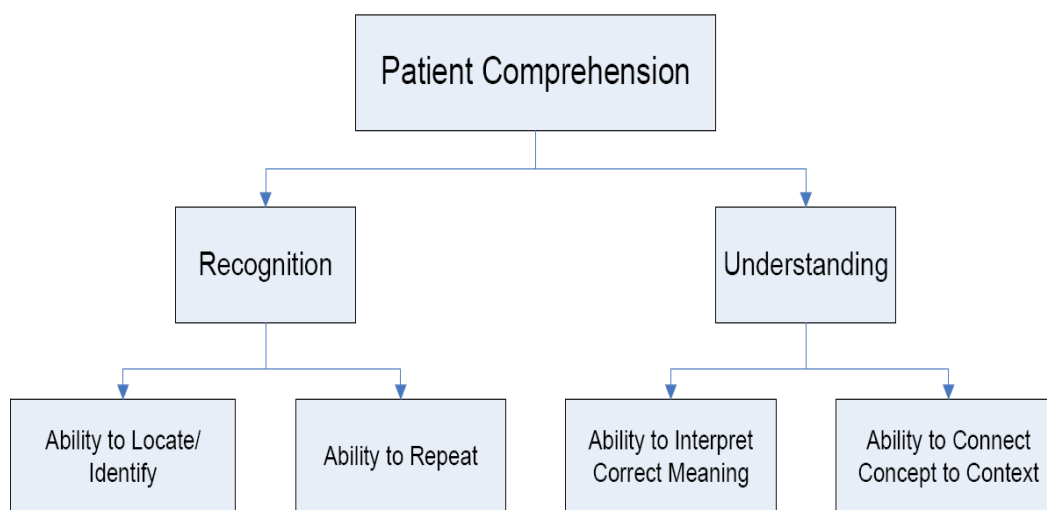


Figure 1. Patient functional comprehension assessed domains by action.

and specific actions. The ability to recognize a concept includes two actions. First, the patient must locate/identify information through reading and/or visually scanning the text. Next, the patient needs to demonstrate a capacity to repeat the identified text. An example to illustrate: if a patient was asked “What is the most important information you should know about this drug?” (this is the heading of the first section of most med guides), the patient could look at the med guide, locate the section that lists this information, and then read it aloud to an interviewer. Thus the domain of concept recognition is (1) identify, (2) repeat.

The second domain is the ability to understand a concept. Again, understanding includes two actions. However, for understanding, the actions are closely related. First, the patient must demonstrate the ability to interpret the correct meaning from the text. Next, the patient must demonstrate the ability to connect the concept of the text to the context of the text. For example, if the text states that a drug is prescribed to be taken three times a day, the patient would correctly interpret that statement to mean take the correct dose in three separate instances throughout the day, separated by roughly equal numbers of hours. Similarly, in connecting a concept to the context, if a drug is described as an injection, a patient recognizes that means the drug is supplied through a needle or shot. Again, these two mental processes are highly analogous. Many questions that test the domain of understanding could be argued to test either interpretation or connection to context. Asking questions that test each patient action, or in some cases both, covers the functional domain of understanding. Using items that focus on the domains of understanding and recognition completes the operational testing of patient comprehension.

2.5.2 The Information Processing Model

To evaluate the relationship between med guides and patient comprehension, it is necessary to examine how patients process med guide content. Medication guides, like the vast majority of risk communication programs, are based on the assumption that a prior communication of medication information is required for proper medication decision-making and appropriate medication-taking behavior. Medication guides are one piece—or one communication signal—of a larger risk communication strategy. Adult learning principles and research into effective risk/warning communication agree that the most effective risk messaging consists of multiple signals from multiple sources through multiple channels.^{16, 17, 55, 89} A signal is the outgoing message; a source is the entity responsible for generating or producing the signal; the channel is the communication medium, or the way the signal travels from the source to receiver; the receiver is the signal's recipient.^{16, 17, 55, 89}

The information processing model of health behavior is used because its conceptual framework depicts a root cause of failure analysis of med guides as risk communication tools.⁵⁶ The information processing model presents a human factors framework for examining the process of how a warning message may or may not result in a change in behavior.⁹¹ Specifically, the information processing model demonstrates that a breakdown in the comprehension stage of information processing results in total message failure that will not lead to changes in behavior, in this instance improved patient outcomes.

The information processing model (Figure 2) concentrates on the receiver of the message.²⁶ As the model illustrates, for warning information to be effective it must pass through a successive series of stages within the receiver's consciousness. Each stage builds upon the previous, with failure at any one stage resulting in failure of the warning.²⁶ Wogalter and

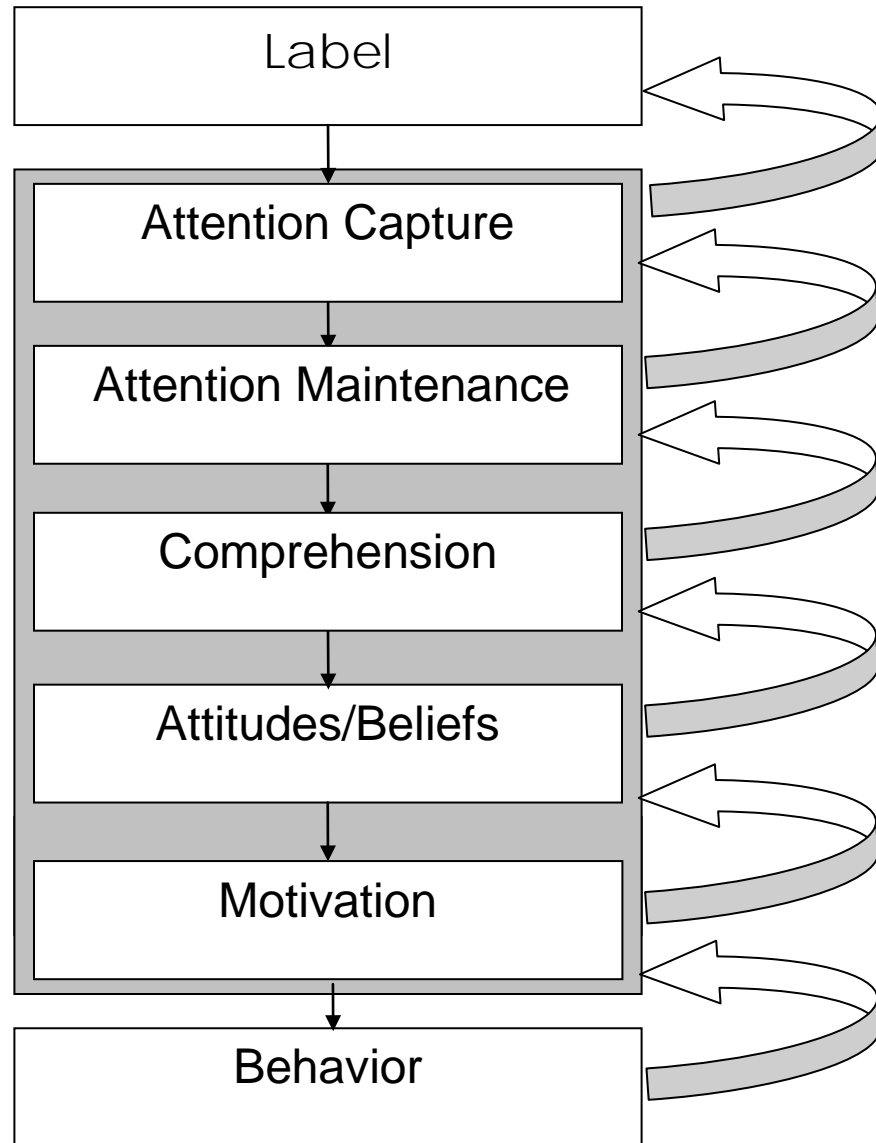


Figure 2: Label Information Processing Model from Wogalter.²⁶

Sojourner adapted the information processing model with respect to human factors information to formulate a model specific to appraising the patient's experience with medication labeling.⁵⁶ As previously stated, medication labeling and med guides function similarly in providing patients information, making the Wogalter and Sojourner's label information processing model appropriate for the present study.

Figure 2 displays the stages of the information processing model. The logic of the label information processing model is that for a med guide to inform decision-making and affect behavior, first it must capture the patient's attention. The signal—here, the med guide—needs to be attended to by the patient in some fashion. The classic example of attention capture in risk communication is a railroad crossing warning signal. At a rail crossing with a train approaching a person encounters posted signs, distinctive flashing lights, loud noise, and a gated barrier. Medication guide attention capture is tempered not only by practical limitations but also by the drug product's ostensible intent to provide the patient more benefit than harm and a signal of unmitigated danger is unnecessary and counterproductive. Next, the patient must maintain attention to the guide for sufficient time to extract information. Attention maintenance on a practical level means the patient makes an attempt to engage the material, essentially the patient tries to read the med guide.

All stages of the information processing model operate in a reciprocal fashion, with each of the lower stages influencing the stages above. Though attention capture and attention maintenance are their own distinct processes, they are also greatly affected by the next stage, comprehension, when the model is applied to technical messages.²⁶ Technical messages, by their nature, are more likely to be formed at a level more appropriate for expert receivers than uninformed receivers.²⁶ Aesthetically, technical messages are even more imposing, or more

confusing, or often both at the same time and less likely to capture and maintain lay person attention. Medication guides are technical documents.^{8, 11} Therefore, the information processing model indicates that a root cause failure is most likely during the comprehension stage of the process.

For example, suppose the med guide distribution process were altered so that each product with a med guide also included an ETASU plan. The ETASU stated that before a drug product could be dispensed to the prescribed patient, the patient was obligated to look at the med guide under the supervision of an HCP for two minutes: Just the patient examining the med guide, uninterrupted for two minutes, and the whole process is to be supervised by an HCP. This alteration would dramatically increase attention capture and attention maintenance. However, if the patient were unable to comprehend the med guide content, even near 100% attention capture and attention maintenance would not result in behavior changes. Comprehension, then, is the essential stage for investigating root cause analysis failure.

In terms of practical understanding, patient comprehension is a higher level of cognitive functioning than patient attention.²⁶ For instance, a patient may pay attention to a med guide by looking at the text and flipping through the pages. However, to comprehend the information in the med guide the patient needs a more in-depth degree of understanding. Patient comprehension will not occur if the information extracted conflicts with preexisting attitudes or beliefs about the medication or its use. Then, the patient's understanding of this information—in conjunction with the patient's attitudes and beliefs—either will or will not produce motivation for appropriate medication-taking behaviors. Lastly, motivated patients may or may not take the final step and actually engage in the behavior. At any point in the series, patient confusion, misunderstanding, misinterpretation, failure to comprehend, bias, or other circumstance will create what Wogalter

termed “a bottleneck” and will not allow for completion of the information processing sequence.⁵⁶ Essentially, the message fails.

Applying a structured interview method within the larger conceptual framework of the label information processing model is likely to pinpoint the root causes of comprehension failure of med guides. Structured interviews are a research method consistent with the label information processing model. Structured interviews, also called structured cognitive interviews, are designed for a researcher to assess a subject’s responses when the subject is questioned on a specific issue or stimulus.⁹² Structured interviews allow for identification and data collection on response patterns, recall, sources of difficulty, effects of context on answers, numeracy skills, and subject interpretation.

2.6 Implications of Medication Guide Research

Evaluating patient comprehension of med guides with respect to health literacy is necessary to improve future risk communication and patient safety efforts and thus reduce the impact of medication errors. As stated previously, although there are numerous studies on med guides, there are surprisingly few studies that directly assess a patient’s ability to read and understand the information contained in the med guide. A search of the *Medline* and *Academic Search Premier* online databases returned no relevant studies when querying “medication guide” together with “health literacy.” In September of 2009 the FDA released an issue statement identifying the urgent need to assess current written patient information formats and objectives.⁵⁷ This study meets that identified need. Moreover, it will assist in the improvement of written patient information by demonstrating the effect of health literacy skills on patient comprehension.

3. METHODS

3.1 Research Design

This was a cross-sectional survey study conducted at primary care clinic sites. The study assessed current understanding of existing med guides through structured patient interviews. Face-to-face interviews were conducted by a trained researcher with a recruited patient. Structured interviews allow for the direct assessment of abilities and degree of understanding related to a given task.^{21, 36} They are a commonly used method in health literacy research.^{17, 32, 93, 94} In this study, structured interviews were employed to determine patient comprehension of med guide content, areas of comprehension failure, level of health literacy, previous medication behaviors and history, health history, socioeconomic status (SES), and other demographic information.

3.2 Patient Participants

Research participants were adult patients in the primary care clinic at the study site who were registered for an appointment. Patients were eligible to participate in the study if they were (1) 18 years of age or older and (2) fluent in English. Several factors were cause for patient exclusion from participating. First, a hearing or visual impairment that was not correctable made someone ineligible because the impairment prevented the person from viewing the materials and/or responding to the interviewer's questions. Next, a patient who was too ill to participate at the start of the interview was excluded. Lastly, patients needed to score a minimum of four on the Six-Item Screener (SIS).

The SIS is a previously validated tool for assessing cognitive impairment among potential clinical research participants.⁹⁵ The SIS is a brief but highly reliable instrument with results that are comparable to the longer mini-mental state examination (MMSE). Six brief questions are

asked to assess temporal orientation and short-term memory recall. Cut-off scores are based on the greater likelihood that the participant may have moderate to severe dementia. When evaluated in the diagnosis of moderate to severe dementia, a cut-off score of three or more errors was associated with a sensitivity and specificity of 88.7 and 88.0, respectively.⁹⁵ The current study excluded patients if they scored three or more errors on the SIS. Using a score of three or more errors purposefully includes patients with the potential for mild dementia on the SIS because mildly demented adults often are primarily responsible for their own health care decisions, including their medication decision-making. Additionally, past research demonstrated that many low SES patients will score at the mildly demented level even when their cognitive skills are intact.⁹⁶ Likewise, such patients are also responsible for their own medication decision-making.

The relatively limited exclusion criteria for this study increased the number of patients with limited health literacy who also make their own medication decisions. Subjects could withdraw from the study at any time with no negative consequences. Other than patients with limited health literacy, no special or vulnerable populations were specifically recruited.

3.3 Patient Recruitment

Patients were recruited from the waiting room area of two primary care clinics. Recruitment took place during weekday business hours when the clinics were moderately busy. Moderately busy meant patient numbers were high enough to make it likely some persons would want to participate but not such a prohibitively high number that there would be no available space in the clinics to conduct the interviews. A clinic staff member trained in the study's recruitment protocol first identified potential participants on the basis of age and whether the person spoke English fluently. The staff member was well-positioned to gauge these

characteristics and also was aware if the person's appointment was concluded. Next, the staff member used a recruitment flyer approved by the Institutional Review Board (IRB) to approach the patient. This flyer can be seen in Appendix A. The flyer was written at the sixth-grade reading level. It contained the basic information that the survey was about how people learn about medicines, it would take about 25 minutes to complete, and participating would provide \$20 compensation for the patients' time and effort. The primary investigator's name and contact information and site IRB approval were also clearly visible.

When a patient expressed interest in participating, the clinic staff member directed the patient to the interviewer. The interviews were conducted in a private room, typically an unused patient exam room or office in the clinic. The interviewer first provided the patient with an information sheet (Appendix B). This sheet provided the patient the name of the project, the participation criteria, the parts of the interview, a clear statement noting this was voluntary research, and the primary investigator's contact information. Regardless of participation, the patient was given this information sheet to keep. Next, the interviewer assessed the patient's age and confirmed the patient understood English. Then the interviewer initiated the SIS. If the patient scored three or more errors, the patient was unable to participate. If the patient scored two or fewer errors, the patient was told he or she was eligible to participate and the approved verbal consent process was started. According to UIC IRB standards, verbal in lieu of written consent was most appropriate for this research because of (1) the limited risks anticipated with participating and (2) the signed consent form would be the only item that would contain the patient's name. The interviewer read an IRB-approved verbal script to the patient (Appendix C). This script included the sponsor of the research and the primary investigator's relationship to the sponsor. A risk disclosure was provided, as were potential benefits to the patient and a statement

regarding protection of the patient's anonymity. A clear statement of the voluntary nature of the research and that the participant could stop at any time was provided again. Lastly, the patient was asked to verbally consent to participation.

3.4 Research Procedure

The structured interviews were conducted by research assistants (RAs) trained on the full research protocol. All RAs were trained how to administer the steps of the interview in a consistent manner. Prior to recruiting patients, RAs role-played interviewing each other as patients and then appraised performances to check for consistent application of the survey amongst one another. Additionally, at a minimum of once a week, RAs discussed any interviewing issues.

After obtaining consent, RAs conducted the survey. If the patient was unable to complete the survey for any reason, the incompleteness was noted both in the survey file itself and on the RAs' data collection log. The survey was administered and responses were recorded using the Snap Interviewer software program.⁹⁷ The software provided several advantages for recording health science interviews. First, the Snap Survey was built to simultaneously display to the interviewer the exact text that should be said to the patient at each stage of the interview while also allowing for directions to the interviewer himself or herself. Next, the Snap Survey was customized to include closed- and open-ended questions. It also allowed for verbatim answer transcription for each question. Because the interviewer entered the patient's responses verbatim in addition to coding the responses, it was possible to return to a specific response in the instance of a coding issue. Lastly, the software produced a text file of answers to allow for efficient data collection and comparison of the quantitative and qualitative responses.

3.5 Survey Instrument

The survey used in the structured interviews was a composite tool that used an original question design in addition to sets of questions previously developed and validated from research on med guide comprehension and health literacy. The complete survey with correct answers marked is found in Appendix D. After the informed consent, the survey contained five sections. Each section contained a mixture of short answer questions. Section 1 solicited the patient's medication experience.

Sections 2, 3, and 4 provided the patients with existing, FDA-approved med guides and assessed their comprehension of each guide's content. Section 2 provided the patients with a med guide for Ritalin, an oral tablet drug formulation. Section 3 provided the patients with a med guide on morphine sulfate oral solution. Section 4 provided the patients with a med guide on an injectable, Aranesp. Because the purpose of the study was to gauge patients' comprehension of the information contained in med guides, it was important to choose guides that were representative of all current available guides.

All 227 med guides available and posted to the FDA website as of May 2010 were appraised according to three criteria: readability according to Lexile analysis, word count, and frequency of prescriptions in the U.S. First, all med guides were assessed according to Lexile score. Lexile scores are based on word frequency and sentence length, with greater values indicating text that was more difficult to read. Medication guides were ranked according to Lexile score. Next, all med guides were examined and ranked according to total word count. Last, the relative frequencies of prescriptions of the 227 med guide drug products were obtained from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.^{98, 99} Confidence intervals were established for Lexile score and word count

to identify the drug products within one standard deviation of the mean score for both of these criteria. This shortened list was cross-referenced with drug products in the top 50% of frequently prescribed medications in the U.S. The result was a list of 26 med guides that were of average readability and length and were among the top 50% of most prescribed drugs in the U.S. From these 26 guides, three were chosen at random for use in the study, one from each of three common routes of administration—oral tablet, oral liquid solution, and injectable. Specifically, the guides chosen for inclusion were for Ritalin, morphine sulfate oral solution, and Aranesp, respectively.

First, the patient was handed the med guide and asked to review it. The patient was told he or she could continue to look at the med guide at any time. A digital timer was used to keep a record of the patient's total time to complete each of the three med guide survey sections. To start, the patient was given 2 minutes to review the guide without interruption at the beginning of each section. Two minutes was chosen as the independent reading time based on the focus on patient comprehension in the short-term, as described in Section 2.5.1 above. At the end of 2 minutes, the patient was asked to answer a series of questions. The questions were derived directly from the main content areas of the med guide: most important information for patients, side effects, warnings, contraindications, storage, and general information. The questions required the patients to demonstrate their ability to search the text and to extract content of varying complexity. Patients were also asked to make inferences about the use of the specified medication. For instance, the patients were asked about the appropriate response if a particular side effect or symptom occurred. Moreover, patients were asked to apply their own health literacy skills and/or numeracy skills to extract and implement the content of the med guide in situational circumstances that were common to patients taking the medication. For example, if a

med guide stated the medication must be taken 30 minutes before meals, the patient was asked what time he or she would take the medication if he or she planned to eat breakfast at 8 AM. Questions were grounded to help patients more easily respond, that is, the patient was asked for a specific instead of a general response (e.g., “name three possible side effects associated with taking this medicine” instead of “name as many side effects as you can”). Responses were regarded as incorrect if they were inaccurate or incomplete. Survey coding of responses will be described in more detail in Section 3.6 below. At the end of testing the comprehension of content, each med guide section asked the patient to state the most important thing the patient should know about the drug according to the guide. Verbatim answers were captured. Prior use or experience with the medication were the last four questions for Sections 2, 3, and 4. A patient’s prior experience with a medication was an important potential confounder that was captured for each medication.

Appendix D presents the survey instrument. Each survey question is listed, with the correct response(s) identified. Several questions for each of the med guides required patients to identify multiple correct responses for a single question; for example, “What are five of the most common signs of withdrawal from morphine sulfate in adults?” Any of the responses listed below the question is correct. The RAs marked the first five correct responses the patient provided. Patients received a score from 0 to 5 for this question. For the Ritalin med guide the survey included 12 questions with 33 total possible correct answers. For the morphine sulfate guide, patients were asked 15 questions that had a possible total of 32 correct answers. For the guide about Aranesp, the assessment comprised 12 questions with 34 possible correct responses.

Data were collected on a full set of covariates in Section 5. First, patient personal health background and characteristics were assessed, including basic demographics (age, gender, and

race/ethnicity) and SES information (education, household income, and employment status).

Also, patients were asked to self-report their health status and health services utilization information. Previous research showed strong agreement between patient self-reports and medical records for hypertension, heart failure, diabetes, cancer, and stroke.^{100, 101}

Section 6 assessed patient health literacy using the Rapid Estimate of Adult Literacy in Medicine (REALM). The REALM is a reading recognition test composed of 66 health-related words, and it is the most commonly used assessment of patient literacy in medical settings.^{21, 102} Administering the REALM involves having patients read aloud from the list of medical terms, which are arranged in increasing order of difficulty. It can be administered in less than 3 minutes, and raw scores are calculated by a simple sum of the correctly pronounced words that can be converted into one of four reading grade levels: Level I, third grade or less (0-18); Level II, fourth to sixth grade (19-44); Level III, seventh to eighth grade (45-60); and Level IV, ninth grade and above (61-66). The REALM is highly correlated with standardized reading tests and the Test of Functional Health Literacy in Adults (TOFHLA).^{21, 102} The four reading levels associated with REALM results were collapsed into three levels. Federal guidelines formed on the basis of health literacy's seminal Keystone Dialogues recommended med guides be written at the sixth to eighth grade level.^{2, 3, 12} However, previous health literacy investigations found no med guides that met this recommendation.¹¹ The med guides available in the U.S. as of May 2010 were written almost exclusively at the high school reading level and beyond.¹¹ For that reason, the present study defined adequate literacy as being equivalent to the ninth grade reading level or above. For REALM scores low literacy was defined as patients with scores of 0-44, marginal literacy was defined as patients with scores of 45-60, and adequate literacy was defined as patients with scores of 61-66.

3.6 Survey Coding

When interviewing, RAs first selected boxes in the Snap Survey that corresponded to the patient's responses. Next, the RA recorded—where applicable—the verbatim response of the patient. There were several advantages to dual coding patients' responses. The most significant advantage was that the resultant record contained a mixture of quantitative and qualitative data that were analyzed together. Additionally, with the verbatim transcript intact, it was possible to adjust the scoring scheme as the research moved forward. Because what the patient actually said was captured, if the research leadership determined a change were necessary in the coding, all records could be searched for the applicable circumstance and changes made that were consistent for records from beginning to end. For example, one question asked a patient about the best place to store a drug: kitchen cabinet, windowsill, or refrigerator. The correct answer was kitchen cabinet. One RA scored "medicine cabinet" correct, another did not. In this and similar events, all records were examined and a consistent standard applied.

The RAs communicated scoring issues in conference and through e-mail with the project director and each other. Frequent research team communication and coordination supported consistent scoring from RAs. The project director and the RAs identified those survey items with potential scoring discrepancies. A comparison of the verbatim response text to the item score identified inconsistencies among the RAs. The scoring code was then adjusted to correct for any differences between the item's score and the verbatim response. A formal analysis of inter-rater reliability was not performed prior to this correction in the coded data. The primary investigators had final judgment on all coding issues and interpretations.

3.7 Statistical Analysis Plan

The statistical analyses included tactics for the quantitative and qualitative data collected. First, standard descriptive statistics were generated to summarize the data set. This included patient characteristics, most notably the levels of health literacy. Next, the primary outcome measure of patient comprehension was assessed according to number and percentage of correct answers on the survey, including patient comprehension for total performance on the three med guides, patient comprehension according to dosage form of the product, and patient comprehension with respect to four categories of question content: (1) indications for use, (2) side effects, (3) information important before taking the drug, and (4) dosage/storage information. These analyses tested the first hypothesis, patients will comprehend less than 80% of the content of med guides.

Then, regression analysis tested for associations between the primary outcome measure of patient comprehension and demonstrated level of health literacy. Multivariate models examined a full list of appropriate confounding variables, including age, gender, work status, education, income, and prior experience with selected medications. The regression analysis tested the second hypothesis, patient comprehension of med guide content is associated with health literacy, with low levels of health literacy predicting low levels of patient comprehension. All analyses were performed using STATA version 10 (College Station, TX).

3.8 Data Management

Patients were assigned code numbers to preserve their anonymity. None of the data collected in the Snap Survey contained patient names or other information that would make it possible to identify an individual person from the recorded data file. All data files were stored electronically on password protected computers that were available only to the research team.

These computers were kept and remained in locked cabinets when not in use. The interviews themselves were conducted in private rooms within the primary care clinic. The room door was kept closed.

3.9 Institutional Review Board

An Institutional Review Board (IRB) protocol was approved for this research from the University of Illinois at Chicago Office of Protection of Research Subjects (UIC OPRS, Protocol # 2010-0469). An IRB protocol was also approved from Northwestern University Office of Protection of Research Subjects (Northwestern OPRS, Protocol # STU00025028). Appendix E provides the IRB approval letters for each site. Both Northwestern and UIC IRBs approved this research through expedited review as having minimal risk to the participants involved. This is consistent with voluntary survey research that does not retain patient identifying information.

4. RESULTS

4.1 Patient Characteristics

Overall, 490 primary care patients participated in the study according to protocol. Thirty-three of these patients were dropped from the sample due to incomplete interviews. The most common reason ($n = 28$) for an incomplete interview was that during the interview the patient was called away for his or her doctor's appointment and did not return to complete the interview when the appointment was finished. Five patients did not complete the interview due to an illness episode during the course of the interview. In these instances the patient was capable of participating at the start of the interview but during the course of the interview the patient became too sick to continue. Reasons identified included coughing attacks, severe headaches, and in one case a recent stroke victim was unable to stay alert. The interview combined with the patients' conditions was in the judgment of the RA too much stress and could possibly endanger the patients' health. These interviews were stopped and identified as incomplete in the Snap record and in the investigator notes. Four patients were ruled ineligible to participate because they did not meet the entry criteria of age, English-speaking, or failed to score 4 or higher on the SIS. Another four patients were ineligible because they did not have their glasses and could not read sufficiently without them. These 41 cases were dropped and not used in this analysis.

Of the 490 patients assigned a case number, 449 (91.6%) completed the interview. Patients ranged in age from 18 to 85 years old. Patient characteristics are provided in Table I. The mean patient age was 45 ($SD = 14.8$) years. Eighty-five patients (18.9%) were 60 years of age or older. The majority of the patients were women (female = 289, 64.3%; male = 160, 35.7%). Also, the majority of patients were African American ($n = 240$, 53.5%) versus White ($n = 157$, 35.0%) or other ($n = 52$, 11.5%). The largest group of patients reported highest level of

TABLE I

PATIENT CHARACTERISTICS, STRATIFIED BY HEALTH LITERACY LEVEL^{a, b}

PATIENT CHARACTERISTICS, STRATIFIED BY HEALTH LITERACY LEVEL								
Variable	All Patients (n = 449)		Demonstrated Health Literacy Level				P	
			Low (n = 63)	Marginal (n = 63)		Adequate (n = 283)		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	45.3	(14.8)	50.4	(10.7)	46.9	(14.2)	43.6	(15.5)
	%		%		%		%	
Female ^c	64.3		14.2		21.5		64.4	
	Race ^c							<0.001
African American	53.5		23.8		34.6		35.3	
White	35.0		1.9		7.0		91.1	
Other	11.5		5.9		17.7		76.5	
	Years of education ^c							<0.001
High school or less	34.0		32.7		36.6		30.7	
Some college	24.5		8.2		27.3		64.6	
College graduate	41.4		2.2		9.1		88.7	
	Household income ^c							<0.001
<\$20,000	34.8		31.0		35.9		33.1	
\$20,000 to \$50,000	22.5		7.5		20.2		72.3	
≥\$50,000	42.7		3.4		12.4		84.3	
	Employment status ^d							<0.001
Working	55.9		20.6		48.5		66.8	
Not working	43.8		79.4		51.4		33.2	
	Patient identified health status ^d							<0.001
Excellent	14.0		3.2		3.8		20.1	
Very good	29.2		15.9		24.3		33.9	
Good	29.4		36.5		35.9		25.4	
Fair	23.8		34.9		33.0		18.0	
Poor	3.6		9.5		2.9		2.5	
	Previously heard of a medication guide ^d							0.77
Yes	33.9		28.6		32.0		35.7	
No	62.6		71.4		66.0		59.3	
	Medications taken daily ^d							<0.001
None	22.7		4.8		23.3		26.5	
1	21.1		17.5		11.7		25.4	
2	12.9		4.8		13.6		14.5	
3	10.7		12.7		12.6		9.5	
4	7.8		11.1		7.8		7.1	
5	24.7		49.2		31.1		17.0	
	Read instructions before taking prescription medicine ^d							0.006
Always	53.4		39.3		50.5		57.6	
Most of the time	27.6		31.2		30.1		25.9	
Once in a while	15.4		24.6		14.6		13.7	
Never	3.6		4.9		4.9		2.9	

^a Patient groups were stratified according to demonstrated level of health literacy via REALM.^b Regression tests were performed for differences between literacy categories.^c Percentages for this variable were calculated across literacy categories.^d Percentages for this variable were calculated within literacy categories.

education was college graduate (n = 186, 41.4%). About one quarter of patients reported 1 to 3 years of college (n = 110, 24.5%), a little more than one fifth graduated high school but had no additional formal education (n = 103, 22.9%), and about one tenth completed some high school or less education (n = 50, 11.1%).

Patients were asked to provide an estimate of their total household income for the past 12 months. The most common response was over \$50,000 (n = 178, 42.7%). One third of the patients were in households earning less than \$20,000 per year (n = 145, 34.8%), and one fifth earned between \$20,000 and \$50,000 per year (n = 95, 22.5%). Overall, 46% (n = 207) of patients worked full-time, 43% (n = 197) did not work, and 10% (n = 44) worked part-time. On the basis of total household income and the reported number of people supported by this income, approximately one third of patients were below 125% of the Federal Poverty Levels for 2011.¹⁰³

Patients provided a categorization of their health status by answering the question “In general would you say your health is” Patients answered Very Good (29.2%, n = 131) or Good (29.4%, n = 132) almost 60% of the time. Fair was third most common (23.8%, n = 107), followed by Excellent (14.0%, n = 63), then Poor (3.6%, n = 16). Consistent with established health report research, income and health status were positively correlated.

Background health characteristics were assessed by reading the patient a medical condition and asking if a doctor or nurse had ever told the patient he or she had the condition. Patients could respond Yes, No, or Don’t Know. Table II summarizes the identified conditions and their prevalence. High blood pressure (43.2%), arthritis (31.9%), high cholesterol (31.2%), depression (22.7%), asthma (21.9%), and diabetes (18.5%) were the most identified conditions. Heart attack (5.7%), stroke (7.8%), heart failure (6.0%), and other serious cardiac conditions were reported by fewer than 10% of patients. Cancer was reported more rarely, (4.5%).

TABLE II
BACKGROUND HEALTH CHARACTERISTICS,
STRATIFIED BY HEALTH LITERACY LEVEL^{a, b, c, d}

Medical Condition	All Patients (n = 449)	Demonstrated Health Literacy Level			P
		Low (n = 63)	Marginal (n = 63)	Adequate (n = 283)	
	%	%	%	%	
Heart attack	5.7	15.9	6.8	3.2	<0.001
Stroke	7.8	17.5	12.6	3.9	<0.001
Heart failure	6.0	15.9	10.7	2.1	<0.001
Enlarged heart	3.1	4.8	5.8	1.8	0.18
Diabetes	18.5	33.3	10.7	5.7	0.001
Fluid in the lungs	8.0	14.5	10.7	5.7	0.02
Chronic bronchitis	9.6	19.4	11.7	6.7	0.001
Heart bypass or angioplasty	2.7	6.5	4.9	3.9	0.51
Asthma	21.9	30.7	26.2	18.4	0.02
Emphysema	2.7	9.7	2.9	1.1	<0.001
High blood pressure	43.2	73.0	51.5	33.6	<0.001
High cholesterol	31.2	55.6	35.9	24.1	<0.001
Angina	7.3	20.6	12.6	2.4	<0.001
Arthritis	31.9	55.6	36.9	24.7	<0.001
Cancer	4.5	3.2	7.8	3.5	0.57
Depression	22.7	41.2	26.2	17.4	<0.001
Cataracts	4.7	4.8	4.8	4.6	0.82
Trouble hearing	11.6	20.6	11.7	9.6	0.02

^a Background health characteristics were assessed by patient self-report.

^b Patient groups were stratified according to demonstrated level of health literacy via REALM.

^c Regression tests were performed for differences between literacy categories.

^d Percentages are reported according to patients who answered positively to ever having the listed condition.

The SIS assessed patients' cognitive awareness. With a minimum score of 4 out of the 6 items correct needed to participate, the mean score of the enrolled sample was 5.8 (SD = 0.43), with over 80% of patients scoring 6 out of 6. Only nine enrolled patients scored a 4 on the SIS. This number is too few to identify any trends regarding patients with potentially mild dementia and their use of med guides.

There were statistically significant demographic differences between the sample population at clinic site #1 (n = 223) and clinic site #2 (n = 226). Table III presents these differences. The population at clinic site #1 was primarily African Americans, who had a high school or some college education and low income. Clinic site #2 was primarily White college

TABLE III

DIFFERENCES IN PATIENT CHARACTERISTICS BY CLINIC SITE^{a, b}

DIFFERENCES IN PATIENT CHARACTERISTICS BY CLINIC SITE					
Variable	Clinic Site #1 (n = 223)		Clinic Site #2 (n = 226)	P	
Age in years, mean (SD)	46.7	(12.9)	43.9	(16.3)	<0.01
Female, %	68.1		60.6		0.10
Race/ethnicity, %					<0.001
African American	89.7		17.7		
White	4.5		65.0		
Other	5.8		17.3		
Years of education, %					<0.001
High school or less	61.0		7.5		
Some college	29.1		19.9		
College graduate	9.9		72.6		
Household income, %					<0.001
<\$20,000	64.4		9.0		
\$20,000 to \$50,000	24.2		21.0		
≥\$50,000	11.3		70.0		
Employment status, %					<0.001
Working	39.5		72.1		
Not working	60.1		27.9		

^a Patients were recruited from two separate clinic sites at different urban academic medical centers.

^b Chi-square tests were performed for differences in characteristics between patients at Clinic Site #1 and Clinic Site #2.

graduates with an income of more than \$50,000 annually. These characteristics are consistent with the larger patient populations these clinics serve. These characteristics are also consistent with the design of the study; the intent was to use two clinic sites to recruit a diverse range of patients.

4.2 Medication Use History

At the start of the interview, only one third (33.9%) of patients reported having heard of a med guide previously. Alternatively, over 80% of patients reported that before they take prescription medicines they Always (53.4%) or Most of the Time (27.6%) read the instructions for use. More than three quarters of patients reported taking at least one prescription drug on a daily basis (77.3%) and one quarter of patients (24.7%) reported taking five or more drugs on a daily or almost daily basis. Over-the-counter (OTC) medications, vitamins, supplements, or herbal remedies taken daily or almost daily were less common, with nearly 65% of patients taking none or one. These results are in Table I.

Patient prior experience with the selected med guide medications was captured as a potential confounder. Patient prior use was assessed by asking the patient if he or she was currently taking the drug in the med guide he or she just reviewed, previously took the drug, or had a family member that took the drug. If the patient answered positively to a family member taking the drug, the patient was further asked if the patient helped the family member to take the drug. These 3 categories were collapsed into a single category of prior patient experience with the drug reviewed. For Ritalin, 11.1% (n = 50) of patients had prior experience with the drug. The majority of this experience was helping a family member (n = 35). Correspondingly, the RA interview notes make several mentions of patients with children who took Ritalin and the patient administered the drug to the child.

Morphine was the drug with the most patient prior experience. While just 3.0% of patients said they were on morphine at the time of the interview, 20.9% (n = 94) said they had previously been on the drug. More than 23.1% of patients answered Yes to a family member previously on morphine, but less than 5% said they helped the family member to take it. The RA notes indicated several mentions of patients answering Yes and specifying they were on morphine after some form of surgical procedure while an in-patient.

The med guide for Aranesp was the first encounter with this drug for many patients. One patient was currently taking Aranesp and one patient previously took the drug. Four patients previously helped family members to take Aranesp. The total prior experience with Aranesp was less than 2% of the patients interviewed. Overall, 141 patients identified prior experience with the three drugs assessed.

4.3 Health Literacy

Health literacy was measured via the REALM. Health literacy was adequate for 63.0% of the patients interviewed (n = 283). Low health literacy was observed in 14.0% of patients (n = 63), and marginal health literacy in 23% of patients (n = 103). Statistically significant differences were observed for patients in different literacy levels in several measured categories, as seen in Table I. Patients with low literacy skills were more likely to specify an income of less than \$20,000 per year versus a moderate income of \$20,000 to \$50,000 per year or a high income of more than \$50,000 per year ($p < 0.001$). Low literacy patients were more likely to be African American or other non-White race than White ($p < 0.001$). Also, low literacy patients versus adequate or marginal literacy patients were more likely to have a high school or less education than some college attendance or college graduate ($p < 0.001$).

Moreover, patients with adequate literacy identified better health status than those with low literacy ($p < 0.001$). Over 20.0% of patients with adequate literacy identified health status as excellent compared to just 3.2% of low literacy patients ($p < 0.001$) or 3.8% of marginal literacy patients ($p < 0.001$). Patients with low health literacy were also on a greater number of daily prescription drugs per person than those with adequate health literacy ($p < 0.001$). Close to 75% of patients with low literacy patients took three or more prescription drugs daily compared to one third of patients with adequate literacy ($p < 0.001$).

The bivariate relationship between patient comprehension and health literacy was a positive correlation as shown in Figure 2. In this graph, REALM scores were used as a continuous variable to demonstrate the relationship with the continuous outcome variable of patient comprehension. The REALM does not assess patients' understanding of the terms or patients' ability to use those terms correctly, only whether patients can read and pronounce the words correctly. Most importantly, this relationship indicates disparity in patient comprehension scores, even for patients with REALM scores above 60. This means that even for patients with adequate health literacy there was variation in patient comprehension. The converse does not appear true; with the exception of a few outliers, most patients who scored high in comprehension scored high on the REALM.

Each of the assessed background health characteristics was tested to examine differences between the low, marginal, and adequate health literacy patients. Though some conditions were identified rarely, the frequency of each characteristic was at least 5 in each cell. Table II presents the observed differences. Overall, low literacy patients identified having had a medical condition

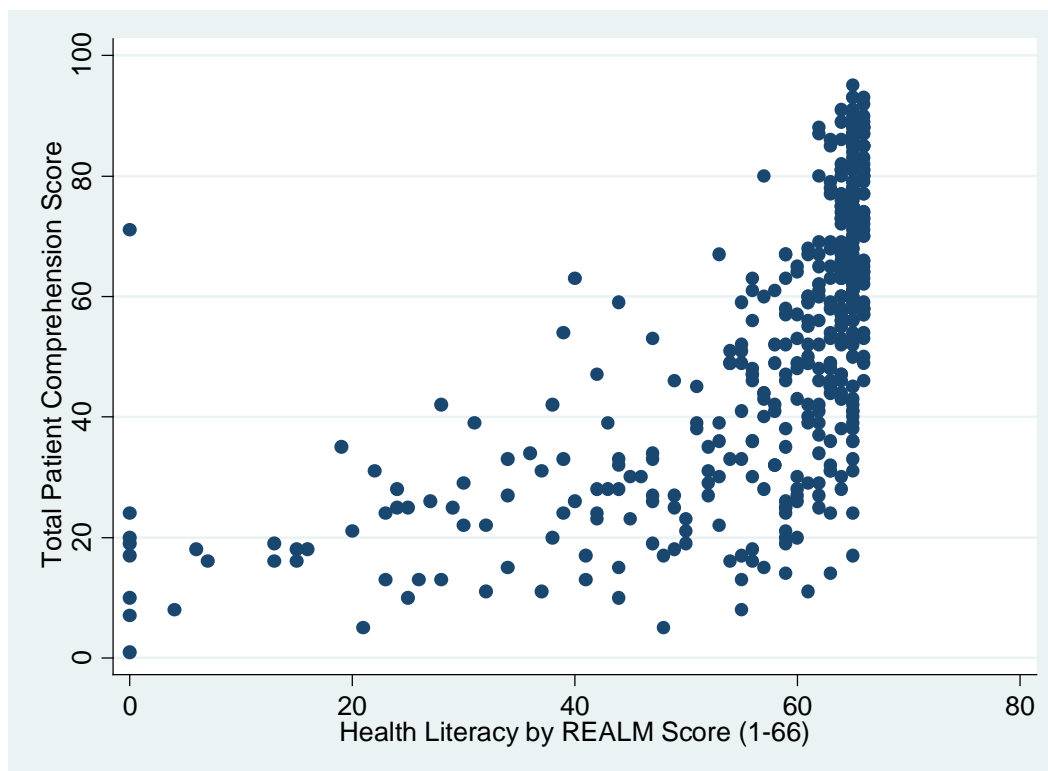


Figure 2. Total patient comprehension by health literacy score on REALM.

more often than the adequate literacy patients in 14 of the 19 conditions asked in the survey ($p < 0.05$). High blood pressure ($p < 0.001$), diabetes ($p < 0.001$), high cholesterol ($p < 0.001$) and arthritis ($p < 0.001$) were reported almost twice as often in the low literacy patients than the adequate literacy patients. Also, low literacy patients reported serious cardiac events, such as heart attack ($p < 0.01$), stroke ($p < 0.001$), and heart failure ($p < 0.001$), four or more times as often as adequate literacy patients.

Several patients were unable to complete any part of the REALM. The RA interview notes indicated that these patients either could not read at all or their literacy skills were impaired to the point where it was not possible for them to engage the REALM assessment. Consistent with prior research, these patients most likely masked their illiteracy throughout the interview by

pretending to read the med guides.⁹⁴ Because the inclusion/exclusion criteria did not discriminate against patients who could not read, these cases were included in the final analysis consistent with protocol.

4.4 Patient Comprehension

Overall patient comprehension was determined by patients' composite scores out of a possible 99 correct responses on the structured interview survey. Results are presented in Table IV. The mean patient score was 52.7 (SD = 22.6) answers correct. This 53.2% correct score average indicates an inadequate degree of comprehension in reference to the established testing standard of 80% or better. Performance ranged among the three different drug formulation guides assessed. For Ritalin, the oral drug formulation, the mean performance was 51.3% (17 out

TABLE IV

PATIENT COMPREHENSION, STRATIFIED BY HEALTH LITERACY LEVEL^{a, b}

Variable	All Patients (n = 449) Mean % Correct	Demonstrated Health Literacy Level			P ^c
		Low (n = 63) Mean % Correct	Marginal (n = 63) Mean % Correct	Adequate (n = 283) Mean % Correct	
Total score	53.2	25.1	38.2	64.9	<0.001
Score on each guide					
Ritalin	51.3	25.4	37.6	62.1	<0.001
Morphine sulfate	60.7	32.9	45.0	72.6	<0.001
Aranesp	49.4	17.5	32.4	60.4	<0.001
Score on categories of question content					
Information important before taking the drug	50.8	22.1	33.2	63.7	<0.001
Indications	60.0	28.8	44.4	70.0	<0.001
Side effects	52.1	24.5	40.7	68.2	<0.001
Dosage	58.3	37.0	48.2	67.7	<0.001
Storage	70.0	54.8	61.7	77.3	<0.001

^a Patient comprehension was the main outcome variable. Patient comprehension was examined as overall score, score on each med guide, and score by question type.

^b Patient groups were stratified according to demonstrated level of health literacy via REALM.

^c Regression tests were performed for differences between low, marginal, and adequate health literacy patients.

of 33) correct answers. Morphine sulfate oral solution had the highest score of patient comprehension, with 60.7% (19 out of 32) correct. Not surprisingly, the least-familiar and most-specialized of the drugs, the injectable Aranesp, had the lowest scores of patient comprehension, with 49.4% correct (16 out of 34). The differences in mean comprehension scores were statistically significant among the three drug formulations ($F = 341.4$, $p < 0.001$).

Patient comprehension was also assessed according to categories of question content. These categories were consistent with the med guide content requirements specified in the Code of Federal Regulations, Section 21 Part 208.³ First, across all the med guides there were 11 questions with a total of 36 correct responses about information important before taking the drug. The mean score was 18.3 ($SD = 9.3$), for 50.8% correct. Also, five questions gauged comprehension of the drugs' indications. On average, patients answered three out of five ($SD = 1.3$) correctly (60.0%). Next, patient comprehension of side effects from med guides was the largest subsection of content, with 48 possible correct responses. This category was much larger than the others because individual questions asked the patient to identify multiple side effects for multiple correct responses. The mean score for comprehension of side effects was 25 out of 48 ($SD = 11.7$), for a mean of 52.1% correct. Dosage comprehension included 6 possible correct responses, with a mean score of 3.5 ($SD = 1.4$) for a mean of 58.3% correct. Lastly, drug storage comprehension was associated with a mean score of 2.8 ($SD = 1.0$) out of 4 items, or a mean of 70.0% correct.

Patient comprehension differed significantly on each measured criterion for patients with low health literacy versus marginal and adequate health literacy, as seen in Table IV. Regression tests were performed for total comprehension score, comprehension scores on each guide, and comprehension scores on categories of question content. Overall, mean total comprehension

score for patients with adequate literacy was more than twice that for patients with low health literacy, 64.9% versus 25.1%, respectively ($p < 0.001$). Significant differences were also observed between adequate literacy patients and low literacy patients for comprehension scores on each individual guide ($p < 0.001$). Both groups of patients scored highest on morphine sulfate and lowest on Aranesp. Patients with adequate literacy scored 72.6% mean comprehension on morphine sulfate, 62.1% on Ritalin, and 60.4% on Aranesp. Low literacy patients did not achieve 50% mean comprehension on any guide with scores of 32.9% on morphine sulfate, 25.4% on Ritalin, and only 17.5% on Aranesp.

Score differences were also statistically significant on every category of question content. For indications ($p < 0.001$), side effects ($p < 0.001$) and information important before taking the drug ($p < 0.001$), scores for the adequate literacy patients were close to double those of the low literacy patients. About two thirds of the adequate literacy patients answered correctly versus one third of the low literacy patients. Patient comprehension scores on side effects are particularly noteworthy because this was by far the largest section of question content at nearly half the survey. That percentage of question content is representative of med guide content. On average, patients with low literacy answered 11 of the 48 side effect questions correctly versus marginal literacy patients, who answered almost 20 of the 48 correctly. Patients with adequate literacy did markedly better than both groups but still averaged only 30 out of 48 correct.

4.5 Multivariate Analyses

A multivariate regression analysis was performed to examine predictors of patient comprehension of med guide content. Patient comprehension was the outcome variable, measured as a continuous variable by total score on the survey. The main independent variable was health literacy. Health literacy was measured by total REALM score and then collapsed into

a categorical variable with low literacy as the reference category with marginal literacy and adequate literacy as the alternative categories. Several covariates were also used in the regression. Age was included as a continuous covariate. Age² was also used to check for a nonlinear relationship, with the effect of age on comprehension remaining consistent after a certain age was reached. Next, race was included as a categorical variable. White was the referent category with African American as one alternative category and other, non-White race used as a second alternative category. Gender was included as a categorical covariate with male as the reference and female the alternative. Then education was used as a covariate with three categories. The reference category for education was high school graduate or less education. Alternate category 1 was some college attendance. Alternate category 2 was college graduate. Work status was included as a categorical covariate, with not working as the reference category and working as the alternative. Income was also a categorical covariate included in the regression analysis. Three levels of income were used with yearly household income of less than \$20,000 as the reference category. The next category was income of \$20,000 to \$50,000 and the last category was income greater than \$50,000 per year. The last covariate included was patient prior experience with any of the med guide drug products. Patient prior experience was a categorical variable, with no experience as the reference and positive prior experience as the alternative.

Table V provides the results of the regression analysis. Regression analysis identified health literacy level as a statistically significant independent predictor of patient comprehension of med guides. Marginal health literacy was associated with a positive prediction ($\beta = 9.20$, $p < 0.001$). Adequate health literacy level was the largest effect in the regression analysis ($\beta = 23.58$, $p < 0.001$). Health literacy level impacted patient comprehension after controlling for age,

TABLE V

**MULTIPLE LINEAR REGRESSION OF TOTAL COMPREHENSION SCORE ON
HEALTH LITERACY AND DEMOGRAPHIC COVARIATES^a**

Variable	Total Patient Comprehension Score	95% Confidence Interval	P
Health Literacy Level_Marginal	9.2 ^{***}	(4.69 to 13.75)	<0.001
Health Literacy Level_Adequate	23.58 ^{***}	(18.92 to 28.23)	<0.001
Age	-0.09	(-0.69 to 0.50)	0.76
Race_African American	-9.45 ^{***}	(-13.14 to -5.75)	<0.001
Race_Other	-6.33 ^{***}	(-10.78 to -1.88)	0.005
Gender_Female	2.06	(-0.73 to 4.85)	0.15
Work Status_Not Working	-1.30	(-4.60 to 1.99)	0.44
Education_Some College	10.29 ^{***}	(6.44 to 14.14)	<0.001
Education_College Graduate	14.55 ^{***}	(10.11 to 18.99)	<0.001
Income_\$20,000 to \$50,000	2.68	(-1.68 to 7.03)	0.23
Income_≥\$50,000	4.49	(-0.10 to 9.09)	0.06
Prior Experience with Drug	2.39	(-0.40 to 5.19)	0.09
Constant	38.54 ^{***}	(24.21 to 52.87)	<0.001
Observations	417		
R ²	0.67		
Adjusted R ²	0.66		

*** p < 0.001.

a A linear regression model examined the associations between patient comprehension and the identified predictive variables. The variable listed and respective β value indicate change from the referent category. The referent categories are Health Literacy_Low Literacy, Race_White, Gender_Male, Work Status_Working, Education_High School Graduate or Less, Income_<\$20,000 Per Year Annual Income, Prior Experience_No Prior Experience With Drugs In Med Guides.

gender, work status, race, education level, income, and prior experience with the assessed drugs. Patients with low health literacy demonstrated significantly lower levels of comprehension than patients with adequate health literacy or marginal health literacy.

Other factors significantly associated with patient comprehension included race, education, and income. African Americans had lower comprehension scores than the reference group (White; $\beta = -9.45$, $p < 0.001$). Other race, defined as non-White and non-African American, also had lower rates of comprehension than Whites ($\beta = -6.33$, $p < 0.01$). Also, higher levels of education were associated with better patient comprehension. Graduating college ($\beta = 14.55$, $p < 0.001$) was predictive of increased patient comprehension, as was attending but not graduating college for a period of time ($\beta = 10.29$, $p < 0.001$).

Neither age nor age² was found to significantly influence patient comprehension in the multivariate regression analysis. Age trended towards a negative effect ($\beta = -0.09$, $p = 0.76$), but it was difficult to identify among the other covariates. The relationship between patient comprehension and age is more clearly seen in a bivariate plot of the two continuous variables found in Figure 3. The line of best fit indicates a negative trend of advancing age on patient comprehension score. Primarily this is a product of most of the top-scoring patients being under the age of 40.

Gender was not significantly associated with comprehension, although being a woman trended towards increasing patient comprehension ($\beta = 2.06$, $p = 0.15$). Similarly, patient prior experience trended towards improving patient comprehension slightly ($\beta = 2.39$, $p = 0.09$). Lastly, work status was not a significant covariate ($\beta = -1.30$, $p = 0.71$).

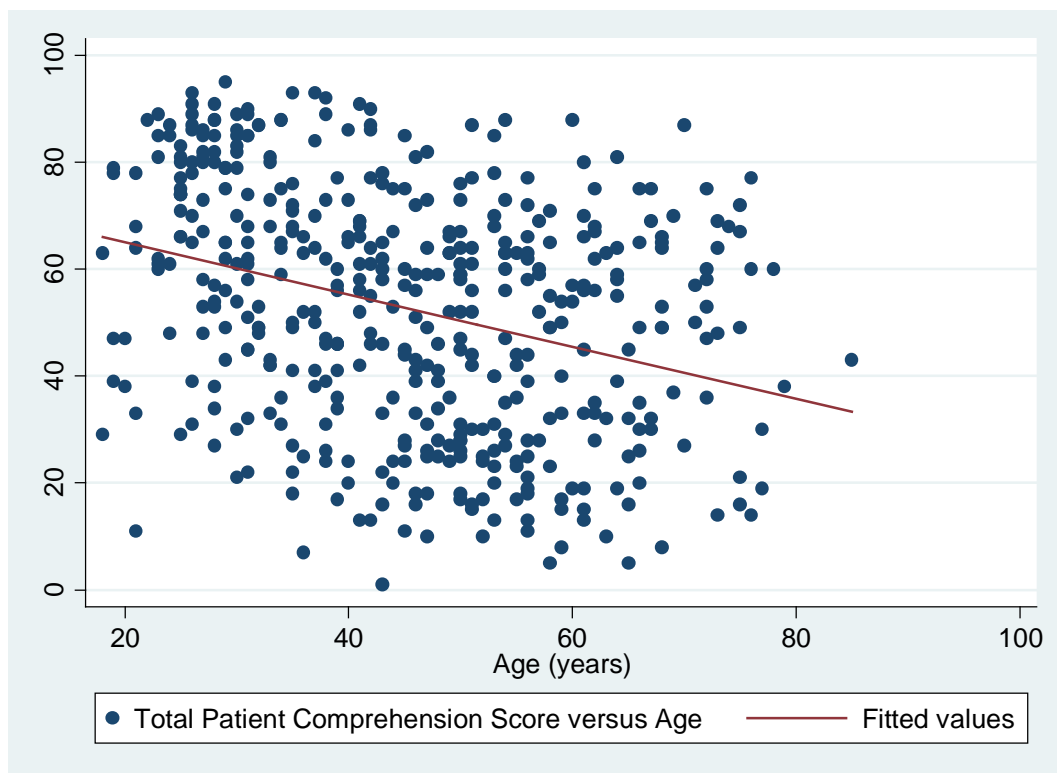


Figure 3. Total patient comprehension score (0-99) plotted by age (years). The line of best fit indicates a negative trend of advanced age associated with lower comprehension score.

5. DISCUSSION

5.1. Patient Comprehension

Patient comprehension of med guides was inadequate with respect to the standard level of comprehension necessary for informed decision-making. Overall, only 62 of the 449 patients comprehended 80% or greater of the med guides content, or less than 14% of patients interviewed. The average mean score correct was not above the 80% comprehension threshold for any grouping of patient characteristics measured. For instance, patients with adequate health literacy, who graduated college, and whose income was more than \$50,000 per year did not meet the comprehension standard (mean 70.9%, SD = 14.0). Stated another way, even patients without the numerous and common risk factors known to impair comprehension of written patient information were unable to comprehend med guide content to the level consistent with risk communication guidelines. The demonstrated rate of poor comprehension even among patients who typically would be classified as highly capable is a clear signal of the shortfalls of the current med guide standards.

Patients demonstrated inadequate comprehension for each of the three med guides assessed. The differences in mean percent correct for Ritalin as the oral tablet, morphine sulfate as the oral solution, and Aranesp as the injectable were statistically significant, but these data do not support any generalizations about the comparative comprehensibility of med guides for different dosage forms because this study examined only one med guide for each type of dosage form. Ritalin and Aranesp were separated by only a few percentage points at around the 50% comprehension mark. Although the difference was statistically significant due to the large sample size, on a clinical level patients were answering 1 out of 2 questions incorrectly for both Ritalin and Aranesp. Morphine sulfate was higher at 60% comprehension for all patients. Part of

this difference is likely due to patients' increased familiarity with any drug called "morphine." Patient prior experience with morphine sulfate was twice as much as Ritalin and 10 times that of Aranesp. When assessing prior experience, the survey was not able to tell if the patient was replying that he or she had previously used morphine sulfate oral solution or if the patient was answering Yes to having used a different formulation of morphine. The RA notes indicated that patients frequently stated they previously took morphine while an in-patient after a surgical procedure. It is more likely the patient received an I.V. formulation of morphine in these circumstances than the oral solution, but any prior knowledge would still apply to morphine sulfate's indications and side effects.

The similarity of these comprehension scores across drug formulations is more clinically relevant to med guides as risk communication tools than to any differences observed. For any of the drug formulations, patients on average failed to comprehend 40% or more of med guide content. Cumulatively, only 53.2% of med guide content was comprehended by patients. The information processing model identifies this inadequate level of comprehension as a root cause of failure of med guides to reduce medication errors because insufficient patient comprehension leads to what the information processing model terms a bottleneck or stop-gap in the information processing sequence at the comprehension stage. The entire risk message fails due to this bottleneck, not just the message content that patients failed to comprehend. There are two reasons for this.

First, the bottleneck at the comprehension stage does not allow for the med guide information to continue to the next stages of information processing, influencing attitudes/beliefs, and then motivation. The changing of attitudes/beliefs happens through patients cognitively ascribing meaning a comprehended message in a way that is significant to them. This

ascribed meaning—if important enough to the patient—provokes motivation that ultimately leads to changes in behavior. Ascribing significant meaning to a half-understood message is unlikely. For instance, consider a magazine article about politics. If every other sentence of the article were written in an unknown language, comprehension of the article's content would be around 50%. A reader probably would be able to have some sense of the article's content and be able to pick out pertinent facts. But it is highly unlikely the reader would change his or her political position on an issue on the basis of this message. The reader does not necessarily reject the information he or she was able to comprehend but does not internalize it in a meaningful fashion because of the level of incomprehensible content. The information processing model predicts the same breakdown for med guides. Although patient comprehension was the outcome of interest in this study, the goal of med guides is to change patient behavior to improve outcomes. That is unlikely, because failure at the comprehension stage stops the message before behavior is changed.

Second, failure at the comprehension stage leads to total message failure because of the negative effects on the previous stages of attention capture and attention maintenance. To assess patient comprehension in this study, attention capture and attention maintenance were manipulated. Patients volunteered for the study, effectively volunteering their attention. Patient attention was maintained through the interview process with the presence of and questions from the researcher. Also, patients were paid for their participation, giving them incentive to provide both attention capture and maintenance. However, in the clinical setting, failure at the comprehension level in one instance influences future attention capture and attention maintenance. Once a patient identifies the med guide as content that is not useful to him or her, the patient is more likely not attend to the med guide in the future. Risk communication research

predicts a spillover pattern of behavior in these circumstances where persons get in the habit of not attending to any risk communication messages that resemble previously dismissed messages.^{26, 55, 91} This means that a patient who found the med guide to Ritalin incomprehensible is then more likely to not attend to a med guide on a different prescription drug product. Although not directly assessed, this prediction is consistent with the survey data of a low rate of patients who had previously heard of a med guide at the start of the interview (33.9%) despite common daily prescription drug usage by the patients.

Patient comprehension scores by category of question content were consistent with overall patient comprehension scores. As the largest category, mean percent comprehension of side effects, with 48 items, was close to the overall patient comprehension mean, 52.1% and 53.2%, respectively. The indications category provides insight into patient comprehension of the med guide layout. Five items tested patient comprehension of the three drugs' indications, with a mean correct of 60.0%. But this percentage is inflated by 93.5% of patients' correctly identifying morphine is used to treat pain. Morphine is a drug name in more common usage than Ritalin or Aranesp (based on a Lexis Nexis database search of major world newspapers from 2010).¹⁰⁴ Prior knowledge heavily influenced the morphine indication item. Ritalin's two indications were identified by 41.2% of patients correctly and Aranesp's indication by only 17.2% of patients. When patients are unfamiliar with a drug, most of them cannot find what the drug is used for in the med guide. This is remarkable given that a drug product's stated indication is the most significant single piece of information from a regulatory standpoint.

An NDA is submitted and a drug approved on the basis of its use for a specified condition in an identified population.⁵⁹ This indication is the licensure outcome of the drug product's research and development—and associated millions if not hundreds of millions of

dollars in costs—and the basis for all branded marketing. But in the only piece of written patient information reviewed by the FDA the majority of patients cannot identify what the drug is used for.

5.2 Health Literacy

Patient comprehension of med guide content was significantly associated with health literacy, with a lower level of health literacy predicting lower patient comprehension. In multivariate analyses, health literacy level was the most influential independent predictor of patient comprehension. Low literacy was predictive of comprehension scores roughly 10% lower than patients with marginal literacy and almost a quarter lower (23%) than patients with adequate literacy, when accounting for the effects of other variables.

The positive association between patient comprehension and health literacy score shown in Figure 2 is consistent with the larger regression model demonstrating health literacy is a significant predictor of patient comprehension, and that patient comprehension is also influenced by other factors. However, even at the highest level of health literacy, there is significant variability in rates of comprehension, indicating that there must be other, unmeasured factors, in addition to health literacy, that explain this variability among patients with the same REALM score. Either that or the REALM is not an accurate enough measure of health literacy when assessing patient comprehension because of the REALM's inability to differentiate patients with the highest scores of health literacy.

One factor that did not appear to influence patient comprehension in this study was age. Age was not a significant predictor of patient comprehension in the multivariate regression model. In the bivariate regression with patient comprehension, the scatterplot shown in Figure 3 indicates a trend towards younger patients having the highest recorded total comprehension

scores but overall age appears to have little predictive effect. Age is considered an independent risk factor for impaired cognition, particularly with written patient information because of the associated decreased visual acuity.³⁶ However, that effect was not observed in this study. Fifty-three patients (11.3%) in the study were 65 years of age or older. Patient comprehension score for patients over 65 (47.0%, SD = 20.9) was significantly different than for patients under 65 (53.5%, SD = 22.7), but this difference is more likely due to differences in health literacy and education than age itself. Nonlinear age and patient comprehension relationships were also not significant. Increasing age trends toward decreasing patient comprehension slightly, with the effect leveling off after the age of 65.

Consistent with health literacy, education was also a statistically significant predictor of patient comprehension. Patients identified their highest level of education in free response, and five levels were coded—eighth grade or less, grades 9 to 11, high school graduate, college 1 to 3 years, or college graduate. A clear demarcation appeared between high school graduates and less education and patients who attended or graduated college. Education was divided into these three groups for analysis. College graduation predicted improved comprehension of 15% greater than high school graduates. Patients who attended college for 1 to 3 years showed comprehension 10% greater than high school graduates. Figure 4 shows total patient comprehension mean percent correct scores for these three education levels. What is most notable is that substantial improvement in patient comprehension is found only at the college level. Medication guides are intended as general public risk communication tools, but consistent comprehension is seen only at the college graduate education level. This demonstrates the deficiency of med guides as written patient information for all patients. Although education level and reading level are not

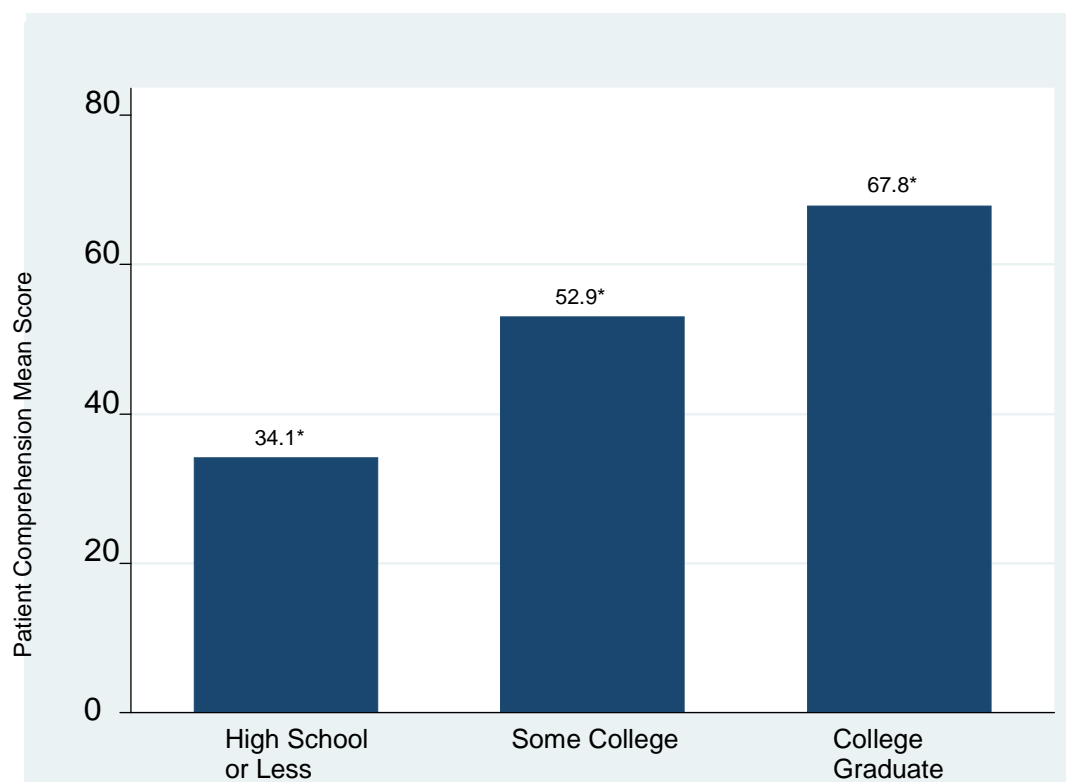


Figure 4. Patient comprehension mean score according to highest level of education. Patient comprehension mean scores differed according to highest level of education reported ($F = 159.1$, $p < 0.001$).

direct substitutes for one another, the federal recommendations for med guides written at the 6th to 8th grade reading level are clearly not met.

Examining patient comprehension by health literacy according to annual income produces a graph analogous to education as seen in Figure 5. The link between education and income is well-established in social science literature and this study's results are consistent.¹⁰⁵ Patients with income under \$20,000 per year have a wide variability of comprehension scores, the majority under the mean average of all patients. Patients with income of \$20,000 to \$50,000 closely mirror comprehension and literacy scores seen in the some college group and scores for patients with more than \$50,000 income per year are consistent with college graduates. Income over \$50,000 per year translated into a positive predictive effect on patient comprehension and income of \$20,000 to \$50,000 trended about half that effect.

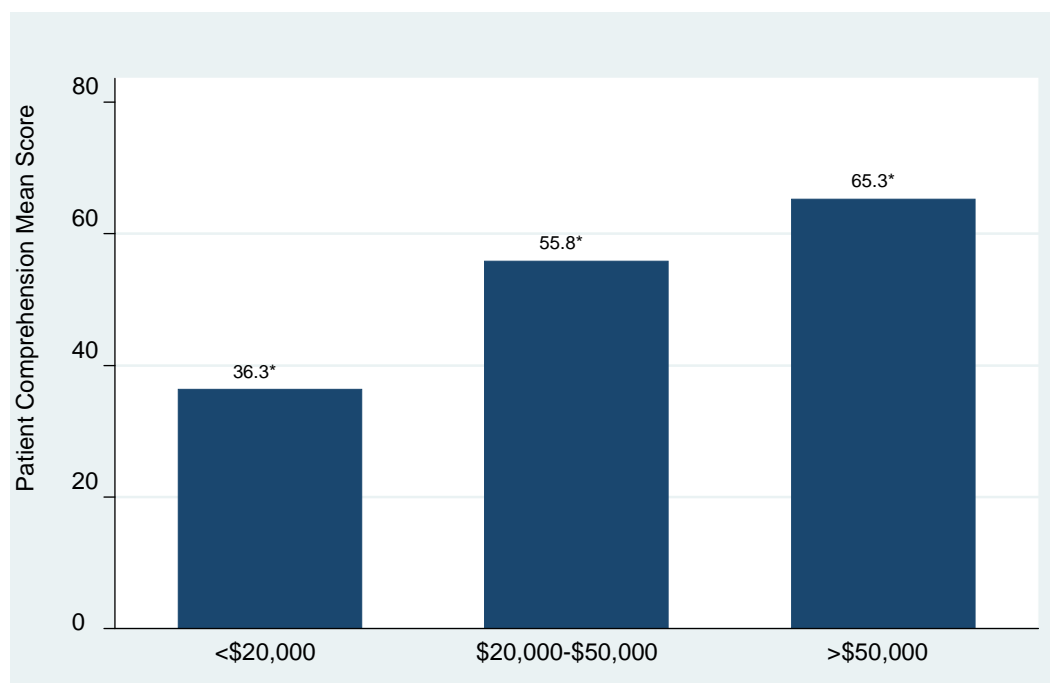


Figure 5. Total patient comprehension score according to annual income. Patient comprehension mean scores differed according to annual household income ($F = 92.5$, $p < 0.001$).

Working status as measured added little explanatory value to the model and was a poorly fit measure. Education and income covered most of the information that work would capture. Working status was reorganized from not working, working part-time, working full-time to two levels in an attempt to increase its value; the effort was without success. Similarly, prior experience was theorized to be an important potential confounder, but identified no significant information or pattern. Figure 6 shows that the distribution of comprehension scores for patients with and without prior experience do not differ at a statistically significant level. The possible high false positive rate of patient experience with morphine likely confounded the usefulness of prior experience as a variable.

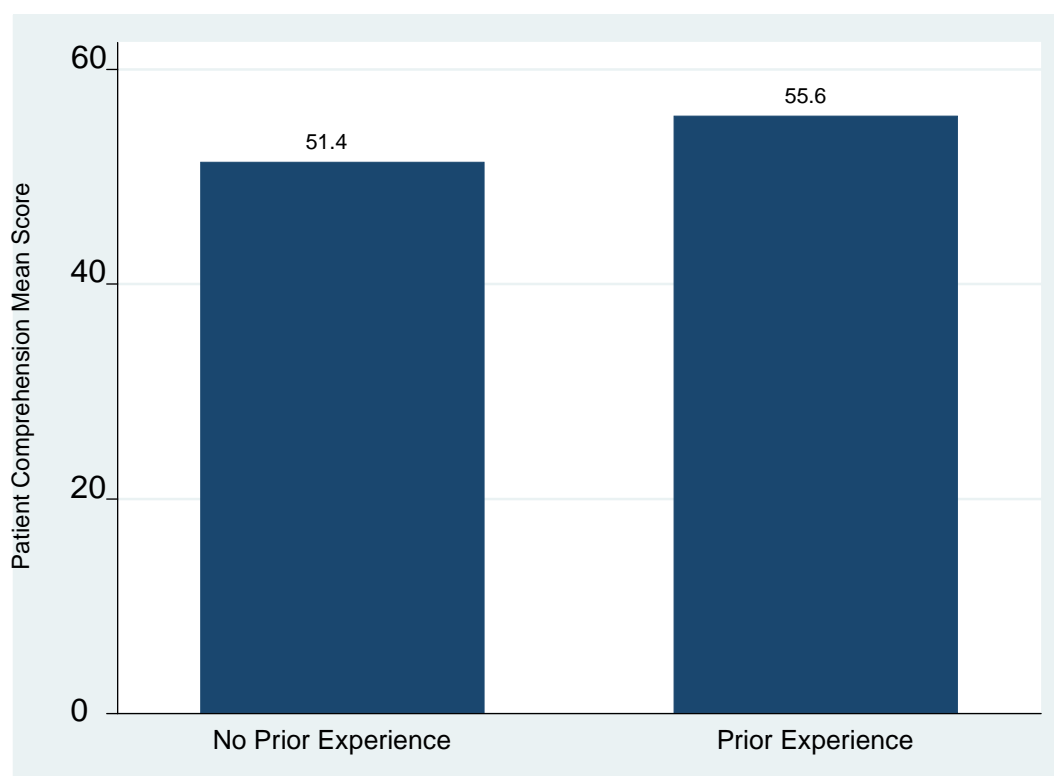


Figure 6. Total patient comprehension score according to prior experience. Patient comprehension mean scores were not significantly different for patients without prior experience with the med guide drugs than for patients with prior experience with the med guide drugs ($F = 3.46$, $p = 0.6$).

Patients displayed important differences with respect to health literacy. Patients with low health literacy were also the patients in most need of drug risk information. Patients with low literacy were in general a less healthy population with more identified chronic and/or serious medical conditions. Correspondingly, low literacy patients took more medications daily with almost 60% on four or more medications. About 40% of marginal literacy patients were on four or more medications daily whereas that number was reduced in adequate literacy patients at 24% on four or more daily. Additionally, patient self-identified health status was much poorer for low literacy patients. The result is that the sicker, more-in-need patient population is less capable of comprehending med guides.

5.3 Patient Familiarity with Medication Guides

At the start of the interview only 33.9% of patients reported ever having heard of a med guide before. This is a surprisingly low percentage given these patients' medical histories and health backgrounds. Forty percent of patients identified high blood pressure, 31.9% indicated arthritis, 31.2% high cholesterol, and close to 20% experienced depression, asthma, and/or diabetes. Many of the prescription drugs commonly prescribed for treatment of these conditions include med guide requirements for dispensing.⁴ Unfortunately, the interview did not assess medication use for a specific condition, only total prescription drugs taken per day.

Noncompliance might explain why these patients recognized they had the condition but were not familiar with the med guide. However, considering this sample of patients were in clinic seeking care, and the mean number of drugs taken per day was 3.3, the more likely scenario is that these patients were on drugs that included med guides but they did not recognize it. This could be due to unfamiliarity with the term *med guide*, lack of attention to the med guide, or failure of the pharmacy to dispense the med guide. Whatever the cause, the 33.9% indicates that for these

patients med guides are not often used as the adjunctive risk communication tool intended in their design and requirement.

5.4 Limitations

This study had several limitations. First, it only examined comprehension as a surrogate marker of safe medication use. It did not examine the association between med guide comprehension and actual medication errors. Reducing the frequency and severity of medication errors is a critical problem that requires efforts at every function of the provision of care. The potential for reductions of medication errors by providing even the most ideal med guides is unknown.

Second, the external reliability—the generalizability of the study’s results to other patient populations—is limited in key regards. A significant limitation to the generalizability of the results is that the interaction between patients and the experimental treatment is different in the experimental environment than the clinical environment. Though actual med guides were used in comprehension testing, the measured patient experience with the guide was different than actual experiences for patients prescribed these medications. The recruited patients often had no prior experience with the medications being evaluated or the conditions the medications are used to treat. This situation challenged the study’s external validity on two key points. First, patients did not experience HCP counseling for a drug prior to receiving the med guide. Counseling and education by physician, nurse, and/or pharmacist provides patients with prior knowledge and context to use to understand med guides.¹⁴ Health care professional counseling creates a mental schema that increases patient’s capacity to comprehend the med guide information.^{56, 106} The effect of patient counseling by HCPs on med guide comprehension is unknown. But consistent with the adult learning principle that comprehension is improved when a message is supplied

multiple times through multiple media and channels, it is likely that HCP counseling prior to receiving a med guide will increase patient comprehension.^{56, 61} Second, patient concentration and motivation may have been greater and may have improved patient comprehension if patients were actually prescribed the drug in question and were reviewing the med guide prior to self-administering the drug. Patients in the experiment were motivated to complete their role in the research study and collect their stipend. Actual patients prescribed a drug may have a greater degree of motivation because of their more personal involvement with the drug product.

The provision of med guides is required as a supplement to and never intended to be a replacement for HCP counseling.^{1, 2, 4, 107} However, med guides by design are intended to act as a source of essential information that patients are capable of using even in the absence of all other information.^{1, 2, 4, 107} Though the experimental circumstances were certainly not ideal, they were not unreasonable.

Additionally, the experimental setting was a much different venue than where a clinic patient would engage a med guide, and it is possible this setting contributed to performance anxiety that could lower patient performance on the survey. Another limitation to the study generalizability was that study participation was limited to patients fluent in English. This was due to use of REALM as the health literacy assessment. A validated version of the REALM is not available in non-English languages. The relationship between written patient information and health literacy for patients without fluent English language skills is important, but it was outside the scope of this study.

Next, all the information the survey captured was patient self-report. The study design did not include a medical chart review to validate patients' medical or prescription history. Previous research indicates patients are likely to make mistakes when asked about their medical

history and current drug regimens. Additionally, selection bias is possible if the patients interviewed were systematically different from the patients who refused or did not participate. The demographics of the populations using Clinic Site #1 and Clinic Site #2 were quite different, but both sites were urban, academic medical centers and it is possible the patients who participated were in some way systematically alike (and different from those who declined to participate). For example, at the start of this study the planned analysis called for a subgroup analysis of patients with mild to moderate cognitive impairment (e.g., patients who scored a 4 on the SIS). However, too few of these patients participated to examine any trends. It is possible that patient recruitment techniques did not accommodate recruitment of these persons but the specific action that may have excluded them is unidentified. Overall, inclusion and exclusion criteria purposefully imposed few restrictions for entrance to increase the representativeness of the sample.

Another limitation concerns the content validity of the operationalized patient comprehension concept. The domains of recognition and understanding and associated patient actions has been validated for evaluating the EMEA standards of patient comprehension for EU written patient information. However, a similar standard has not been set by the FDA for U.S. med guides. Moreover, there are content validity issues concerning the survey instrument itself. Did the individual items collectively capture all relevant aspects of these domains? It is difficult to set a precise domain boundary on patient comprehension as a concept. However, the researchers responsible for the survey designed items that were specific to the content standards that are specified by the FDA for approved med guides under 21 CFR Part 208.21.³ These items were then formatted to be consistent with the EMEA testing procedure.

There was also a concern about the survey's capacity to measure patient comprehension because of the high potential for confounding between measuring comprehension versus prior knowledge. As previously mentioned the independent concepts of comprehension, memory, and prior knowledge are difficult to discriminate in survey measurement. The time limit for initially reading the med guide was employed to reduce the confounding role of long-term memory. However, the survey was limited in its ability to discern whether correct responses were indicative of patient comprehension or prior knowledge. Experience with the drug product was captured in the survey to control for prior knowledge, but it is possible a patient could be without prior experience with one of the med guide drug products but still answer a survey item correctly on the basis of prior knowledge. The most common example of this was high blood pressure and items that asked about side effects. Upwards of 40% of patients identified high blood pressure and when asked for an example of a side effect the patients' response of high blood pressure was naturally an answer they were familiar with as a medical condition. Because high blood pressure was associated with Ritalin and Aranesp on the survey, it is possible there was a systematic pattern by which patients answered items correctly by guessing from their personal experience. However, though this may have affected scores on individual items, the large number of survey items lessens this impact on the overall results.

5.5 Implications

The Plain Language Act of 2010 provides the mandate for the FDA to communicate to the public in a clear, understandable manner free of jargon. Unfortunately, a precise metric to measure performance against this standard is not provided. There is inconsistency from the FDA and health literacy experts in determining parameters for readability of written patient information. Some recommend an 8th grade level or below, whereas others have sought targets as

low as below a 4th grade reading level. Adding to the confusion are more recent debates on the utility of reading formulas altogether, and how much weight should be given to readability as an indicator of a print document's value. Research is needed to identify an operational set of standards for guiding regulators and industry in best practices for designing written patient information such as med guides. These standards are necessary to assess med guide usability for the patient. They should include targets for readability as well as a template to optimize the layout of content.

Like the large number of previous studies that have examined comprehension of health materials, this study found that individuals with lower literacy were significantly less able to navigate and retrieve information and make inferences to support the safe and appropriate use of a medicine. The implication of this is that the patients most in need of additional resources to aid in their decision-making process are the patients least capable of utilizing the information that is currently mandated. Whatever effect a risk communication labeling initiative may have on improving patient experience is lost because of the ineffectuality of the med guide tool. Moreover, because risk communication programs of all sorts but in particular for prescription drugs are generated from a pool of limited resources (i.e., regulatory capacity and funding, HCP time and efforts) the failure of med guides is amplified. The resources spent on med guides are denied another drug safety initiative. Also, not surprising given the degree of difficulty of these med guides and the strong associations with literacy skills, less education was independently linked to poorer functional comprehension. However, one of the most compelling findings of this study was not the results for low literacy patients but for patients with adequate literacy and high levels of education.

As stated in the introduction, med guides are a patient tool often maligned. Anecdotal evidence from HCPs, health literacy experts, and patient advocacy groups assert that med guides are overly complex for most patients. With this prior knowledge, it was reasonable at the outset of this study to hypothesize that patients with low literacy would struggle in comprehending med guide content. But the poor comprehension demonstrated by persons who may be considered a high functioning group—college graduates, patients who scored all correct or just one wrong on the REALM, annual income over \$50,000 and did not possess any risk factors for impaired cognition—was remarkable. At the risk of glibness, the study results for this group may be summarized as follows: Patients who are college graduates, earning \$50,000 a year or more, with few health problems, and experience with medical terms will fail to comprehend the prescription information the FDA deems most important 30% of the time. If this group of patients cannot effectively use med guides, what chance do other patients have of using med guides to inform their decision-making process with medicines? And considering the majority of the U.S. population does not fit into this high functioning group, what is the point of the med guide program in general if it produces written patient information patients cannot use? These findings—when considering other failed sources of written and spoken communication and prescription labeling identified in previous research—underscore the urgency for applying evidence-based, health literacy principles to the re-design of the med guide program.

Another important consideration of this study is the relationship between comprehension of med guides and medication errors. Comprehension of med guides is a surrogate marker for potentially decreasing medication errors and it is a poorly related surrogate. There are three key points in affecting the strength of this relationship. First, the theoretical relationship that increasing patient comprehension decreases medication errors (or stated another way, that

increasing patient comprehension increases/improves patient outcomes) is largely untested.

There is research to indicate that patients who experience a medication error or experience a preventable ADE or demonstrate low adherence typically have low comprehension of prescription information. But a causal relationship between these factors has never been reliably assessed. Any association between patient outcomes and med guide comprehension was beyond the scope of this study. Moreover, because of the complexity (including the number of variables and spurious factors) in assessing how a patient's comprehension of written prescription materials affects patient outcomes, it is unlikely this relationship will ever be fully established.

Next, and following from the lack of a causal relationship, patient comprehension of med guides is a poor surrogate for potentially decreasing medication errors because the effect size of increasing med guide comprehension on decreasing medication errors is unknown. From a risk management perspective, when a potential hazard is identified there are three levels of mitigation to reduce the harm potential. The most effective is to eliminate the hazard through design modification. Second most effective is to physically or procedurally guard against the risk, such as the gate that comes down across a railroad crossing. Several ETASU programs that are part of REMS will have procedural barriers that exemplify physical safeguards, such as blood testing. The lowest effectiveness in mitigating risk is found in warnings or informing of the hazard and the potential harm. The impact of this paradigm is that even the most idealized med guide is limited in its capability to reduce medication errors. No matter how well-matched the med guide is to patient health literacy and information needs, the patients may simply choose to ignore the document. In fact, research in ambulatory pharmacy practices indicate this is often the case.

Finally, the impact of med guide comprehension on medication errors is limited because med guides are a risk communication tool being used in a function over and above risk

communication. Risk communication is defined as effective if patients comprehend the risks and consequences and make an informed decision on how to act. If a med guide informs the patient of serious known risks so the patient is capable of making an informed choice, then a med guide is a successful risk communication tool. But that choice could result in harm to the patient from the medication and this harm would be classified as an ADE. Current use by the FDA of med guides as the most common risk mitigation element in the REMS program positions med guides as a strategy to lower risk of harm from medications, but from a risk communication standpoint a med guide is effective if its intended message is properly transmitted and received, regardless of patient outcomes.

Given the considerable attention recently directed to med guides by the FDA, the Brookings Institution, and the pharmaceutical industry in response to REMS, there now is movement to improve these documents and even seek out a single-document solution for patient medication information. The findings of this study provide the FDA, industry, patient groups, and HCPs with the most compelling evidence to date that quantifies the extent of the inadequacy of current industry guidance for med guides and undisputable proof of the need for the program's revision.

5.6 Future Research Directions

The results of this study are consistent with the conclusions found at a series of patient medication information public workshops hosted by the Engelberg Center for Healthcare Reform at the Brookings Institution in 2010 and 2011. These meetings were a collaboration among senior FDA officials—including CDER Director Dr. Janet Woodcock—health literacy experts, national consumer group representatives, and stakeholders in medical and pharmacy services. The primary consensus formed at these meetings was that the current state of written patient

information, including med guides, is a healthcare system problem and that this problem will require a system solution that includes all stakeholders working in a cooperative effort to improve written patient information. This collaboration and others are making a considerable policy argument for consolidating consumer medication information, patient package inserts, and med guides into a single standardized document termed patient medication information or PMI. The standardized PMI sheet would effectively replace the myriad proprietary information sheets patients receive at retail pharmacies, PPIs, and/or med guides included as part of drug product labeling. Patient medication information is envisioned as a concise, reliable, and valid message capable of providing the patient the requisite risk information in a comprehensible manner.

The obvious difficulty with this plan is how to construct such a PMI document. There is no simple solution to this problem. In written patient information, brevity opposes completeness and consumer-friendly language opposes specificity. Moreover, the FDA is reluctant to take regulatory authority for such a document because it would require a new model of risk communication to set standards and perform the labor-intensive task of determining what risk information *not* to include. This is a task the FDA is unlikely to accept without an increase in budget to do it.

For these reasons the next step in med guide research is to design an enhanced version of the med guide. This process will include the previously overlooked but critical step of evaluating a revised med guide from a human factors research perspective. This research study demonstrated that the content and format standards of the current med guides act as barriers to patient comprehension. The best example of this is the failure of patients to identify the most important information despite the intended prominence of that information in the current content standards. The protocol for designing and pilot testing an enhanced med guide needs to include

an evaluation of how patients actually engage the med guide. This includes evaluating attention capture through observed physical behavior and evaluating attention maintenance through eye-tracking. The inadequacy of patient comprehension demonstrated in this study is a clear signal that the content, style, and format of current med guides require substantial revision to meet the needs of patients. The recommendations of the Keystone Dialogues from 1996 are still viable for improving patient comprehension.¹² However, these goals must be combined with more recent research that demonstrates how to reduce the cognitive load patients encounter with med guides.^{20, 31, 83, 86, 106, 108}

Development of a med guide that more effectively delivers risk information will be an iterative process. There are no known shortcuts to determine the “magic bullet” combination of risk information, length, and format that produces the highest likelihood of patient comprehension.

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APPENDICES

Appendix A

RECRUITMENT FLYER

How do you learn about medicines?



Researchers at UIC are doing a research study to improve how patients learn and get information about their medicine.

Your participation will help!

A research assistant is in the check out area and would like to talk to you right after your appointment. The research assistant will take you to a room close by so you can talk in private. It will take about 25 minutes. You will receive \$20 cash for your time.

Please consider participation in with this important study.

Thank you!

PI Name: Bruce Lambert, PhD
Department of Pharmacy Administration
833 S. Wood Street
[phone number]
IRB # 2010-0469
Project: *Communicating Safe and Appropriate*
Drug Use to Patients and Families

Appendix B

INFORMATION SHEET

INFORMATION SHEET

COMMUNICATING SAFE AND APPROPRIATE DRUG USE TO PATIENTS AND FAMILIES

Written information about certain medicines can be confusing and may need improvement. We invite you to be part of a **research project** to study how patients understand written information about medicines.

To participate, you must: (1) be 18 years or older, (2) enrolled as a patient at the clinic, (3) be English-speaking, (4) have no uncorrectable hearing or vision impairment

The research protocol has been reviewed and approved by the IRB at the University of Illinois at Chicago. There are 3 parts to the interview: (1) questions about current medication guides; (2) questions about general health; and (3) general understanding tests. The interview takes about 25 minutes.

Remember, this is a research study. **You do not have to participate. You may quit at any time without penalty.** There are no risks to you in participating. **If you complete the questions, you will receive \$20 in cash for your time.** Our goal is to recruit a total of 250 participants. Thanks in advance for your time and effort. Send questions or comments to:

Bruce L. Lambert, Ph.D.
Department of Pharmacy Administration
University of Illinois at Chicago
833 S. Wood St. (MC 871)
Chicago, IL 60612-7231
Phone: [phone number]
Fax: [phone number]
Email: [email address]
Cell: [phone number] (while at APhA)

James H. Fischer, Pharm.D., Director
Office for the Protection of Research Subjects
203 Administrative Office Building – M/C 672
1737 West Polk Street
Chicago, Illinois 60612
Phone: [phone number]
Email: [email address]

Location and Schedule for Experiments: The interview will take place after your scheduled appointment in a separate, private room and will take about 25 minutes.

Appendix C

INFORMED CONSENT VERBAL SCRIPT

Date: ____/____/____

ID: _____

Script for Verbal Consent

Hello. I am _____ from the Department of Pharmacy at the University of Illinois at Chicago. I am conducting a research study on how to improve medication guides for prescription medicines. This research project is being funded by Abbott Laboratories. The investigators leading this study, Michael Wolf, PhD at Northwestern University, Stacy Bailey at Northwestern University, and Bruce Lambert, PhD at UIC have served as paid consultants for Abbott Laboratories to support better medication communication. Data gathered from this study may be shared with Northwestern University.

If you choose to participate, I will ask you to complete a private, 25 minute interview with me. You will be given \$20 for your time and effort at the end of the interview.

There is a small risk that you may feel uncomfortable answering the questions I ask you. If you are uncomfortable with any of the questions I ask you, please just let me know and we will skip them. Your participation in this research study is completely voluntary. You can stop the interview at any time. Choosing not to be in this study or to stop being in this study will not result in any penalty to you or negatively affect your right to any present or future medical treatment.

You may not directly benefit from being in this study, but we may learn something that will help us improve medication instructions.

The interview I will complete with you is anonymous. The results of the study may be published but your name will not be known.

Any questions you have about this study may be directed to the principal investigator, Dr. Bruce Lambert, at [phone number]. Questions about your rights as a research subject may be directed to the Office for the Protection of Research Subjects at UIC Institutional Review Board at [phone number]. [give participant card with contact info]

1) Would you like to participate in this study?

a. Yes

b. No

Name (printed) and Signature of Person Obtaining Consent

Date

Appendix D
SURVEY INSTRUMENT

Abbott Study

Thank you for your interest in this study. I have a few questions to see if you can participate.

Patient ID

Interviewer

- ☐ *Amanda*
- ☐ *Ashley*
- ☐ *Interviewer 3*
- ☐ *Interviewer 4*

Date (mm-dd-yy)

Site

- ☐ *Chicago - UIC*
- ☐ *Chicago - Havey*

Appendix D (continued)**SURVEY INSTRUMENT**

1. Do you speak English?

- ☐ *Yes*
- ☐ *No*
- ☐ *Refused*

Appendix D (continued)**SURVEY INSTRUMENT**

Thank you. Unfortunately we can only complete this study with people who speak English. Thank you for your time. (INTERVIEWER: Click next and save answers then submit this interview)

Appendix D (continued)

SURVEY INSTRUMENT

Next, to make sure that you are eligible for the study, I need to ask, how old are you?

(INTERVIEWER: If age outside 18+ range, select here.)

☐ *Not eligible because of age*

Appendix D (continued)**SURVEY INSTRUMENT**

Unfortunately you do not meet the age requirements for the study at this time. Thank you for speaking to me today. (INTERVIEWER: Click next and save answers then submit this interview)

Appendix D (continued)

SURVEY INSTRUMENT

Six Item Screener

Now I will ask you some questions that ask you to use your memory. I am going to name three objects. Please wait until I say all three words, then repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Please repeat these words for me: APPLE - TABLE - PENNY

(INTERVIEWER: Make sure subject correctly hears and repeats all three words before proceeding)

Appendix D (continued)**SURVEY INSTRUMENT**

1. What year is it?

- ☐ Correct
☐ Incorrect

2. What month is it?

- ☐ Correct
☐ Incorrect

3. What is the day of the week? (INTERVIEWER: ex. Monday, Tuesday, etc)

- ☐ Correct
☐ Incorrect

What were the three objects I asked you to remember? (INTERVIEWER: Do not read three items below - check box if remembered or not)

4. Apple

- ☐ Yes
☐ No

5. Table

- ☐ Yes
☐ No

6. Penny

- ☐ Yes
☐ No

7. (INTERVIEWER: Of the 6 above questions, what number were answered correctly?)

- ☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ 6

Appendix D (continued)**SURVEY INSTRUMENT**

Unfortunately, based on your answers, you are not eligible for this study. Thank you for speaking with me today.

Appendix D (continued)

SURVEY INSTRUMENT

Okay. Based on your answers, you are eligible for this study.

**>>READ CONSENT. MAKE SURE IT IS SIGNED BEFORE MOVING
ON<<**

Thank you for participating. We really appreciate your taking time to be involved in this research. First, I am going to ask you a few questions about your medication use. Then I'm going to ask you to read some information about a prescription medication and answer some questions about what you read. Some of the questions have been designed to be difficult, so don't worry if you don't always get 100% correct or aren't sure of the answer. Just do the best that you can.

I can repeat each question only once. If you aren't 100% sure about the answer, just make your best guess and continue.

At the end, I will ask you a few questions about your background and then we'll be done. If you should need a break at any point, please let me know, and if there's anything I can do to make you more comfortable, just ask.

Are you ready to begin?

Appendix D (continued)

SURVEY INSTRUMENT

Medication

First I want to get an idea of how you use medication.

1. Before you take prescription medicines, do you read the instructions for use?

- ☐ Always
☐ Most of the time
☐ Once in a while
☐ Never
☐ Don't know

Other

2. How many prescription medications do you take on a daily or almost daily basis? If you have a list of your medicines with you right now, you may look at it for help in answering this question.

- ☐ 0
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5 or more
☐ Don't know

3. How many over-the-counter medications, vitamins, supplements, or herbal remedies do you take on a daily or almost daily basis?

- ☐ 0
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5 or more
☐ Don't know

4. Have you ever heard of a Medication Guide before?

- ☐ Yes
☐ No
☐ Don't know

Other

Appendix D (continued)

SURVEY INSTRUMENT

Ritalin Questions

I am going to give you a Medication Guide with information about a prescription medication. Then I will ask you questions about that medication. You can look at the materials at any point during the interview. But to begin, please take some time to look over the information, and I'll begin the questions in a couple of minutes.

[START RECORDING TIME]

1. What five types of drugs are MOST important to tell your doctor about before starting Ritalin?

- ☐ Anti-depressants
- ☐ Seizure medications
- ☐ Blood thinners
- ☐ Blood pressure medications
- ☐ Cold/allergy medications

Verbatim Response

2. Please name five of the most common side effects of Ritalin. [score first five responses]

- ☐ Headache
- ☐ Stomach ache
- ☐ Trouble sleeping
- ☐ Nausea
- ☐ Decreased appetite
- ☐ Nervousness
- ☐ Dizziness
- ☐ Heart palpitations

Verbatim Response

3. Is Ritalin addictive?

- ☐ Correct (Yes)
- ☐ Incorrect
- ☐ Refused

Verbatim Response (if necessary)

Appendix D (continued)

SURVEY INSTRUMENT

4. While an adult is taking Ritalin, it is important for their doctor to check what two things often?

- ☐ Heart Rate
☐ Blood pressure

Verbatim Response

5. Under what conditions should someone not take Ritalin?

- ☐ If they are anxious/tense/agitated (or synonyms)
☐ If they have glaucoma
☐ If they have tics/Tourettes
☐ If they have taken an MAOI (must specify beyond anti-depressant?)
☐ If they are allergic to ingredients
☐ If they are younger than 6 years old

Verbatim Responses

6. What are the two main illnesses/diseases that people might take Ritalin to treat?

- ☐ Attention-Deficit Hyperactivity Disorder/ADHD
☐ Narcolepsy

Verbatim Response

7. Where do you think would be the best place to keep Ritalin - in the fridge, in a kitchen cabinet, or on a windowsill?

- ☐ Correct (Cabinet)
☐ Incorrect
☐ Refused

Verbatim Response

8. Before starting Ritalin, a person should tell their doctor if they have problems in what four parts of their body?

- ☐ Heart
☐ Liver
☐ Kidney
☐ Brain/mind

Verbatim Response

Appendix D (continued)

SURVEY INSTRUMENT

9. Say you take Ritalin three times a day (In the morning, afternoon, and evening). You want to eat breakfast at 8am. At what time should you take your morning dose of Ritalin?

- ☐ Correct (7:15-7:30)
☐ Incorrect
☐ Refused

Verbatim Response

10. Among people who do not having existing heart problems before taking Ritalin, what are the four heart-related problems that might happen when they start taking Ritalin?

- ☐ Stroke
☐ Heart attack
☐ Increased/high blood pressure
☐ Increase/high heart rate

Verbatim Response

11. Should a four year old, If they have ADHD symptoms, take Ritalin?

- ☐ Yes
☐ No

Why or why not?

12. If you had a child who takes Ritalin, why should your doctor check your child's height and weight often?

- ☐ Correct (Growth may be slowed/make sure they are growing at an okay rate.)
☐ Incorrect
☐ Refused

Verbatim Response

13. According to this guide, what is the most important thing you should know about Ritalin?

14. [Record time to completion]

Prior Use

Appendix D (continued)**SURVEY INSTRUMENT**

- 15.** Are you currently taking Ritalin?
- ☐ Yes
- ☐ No
- ☐ Refused
- 16.** Have you ever taken Ritalin before?
- ☐ Yes
- ☐ No
- ☐ Refused
- 17.** Has a family member taken this medication before?
- ☐ Yes
- ☐ No
- ☐ Refused
- 18.** Did you help them take it?
- ☐ Yes
- ☐ No

Appendix D (continued)

SURVEY INSTRUMENT

Morphine Sulfate Questions

I am going to give you a Medication Guide with information about a prescription medication. Then I will ask you questions about that medication. You can look at the materials at any point during the interview. But to begin, please take some time to look over the information, and I'll begin the questions in a couple of minutes.

[START RECORDING TIME]

1. Morphine sulfate is used to treat what symptom?

- ☐ Correct (pain)
☐ Incorrect
☐ Refused

Verbatim response

2. Taking morphine sulfate during pregnancy may harm your baby. Name two risks for your baby associated with taking morphine sulfate while pregnant.

- ☐ May cause withdrawal in baby
☐ May cause breathing problems in baby

Verbatim response

3. What is the main reason why you would take the strongest dose of morphine sulfate oral solution?

- ☐ Correct (You are opioid tolerant)
☐ Incorrect
☐ Refused

Verbatim response

4. If you had mild, well-controlled asthma, would it be okay to take morphine sulfate oral solution?

- ☐ Correct (yes)
☐ Incorrect
☐ Refused

Verbatim response

Appendix D (continued)

SURVEY INSTRUMENT

5. What should you do with leftover morphine sulfate when you are done taking it?

- ☐ Correct (*Flush it down the toilet*)
☐ Incorrect
☐ Refused

Verbatim response

6. Does morphine sulfate need to be taken with meals?

- ☐ Correct (*No*)
☐ Incorrect
☐ Refused

Verbatim response

7. You should not take morphine sulfate if you have any of what three health conditions?

- ☐ Allergic to ingredients
☐ Breathing problems/lung problems/sever asthma/asthma attacks
☐ Bowel blockage/paralyticileus

Verbatim response

8. Is morphine sulfate addictive?

- ☐ Correct (*yes*)
☐ Incorrect
☐ Refused

Verbatim response

Appendix D (continued)

SURVEY INSTRUMENT

9. What are five of the most common signs of withdrawal from morphine sulfate in adults?

- ☐ Restlessness
- ☐ Tearing eyes
- ☐ Runny Nose
- ☐ Yawning
- ☐ Sweating
- ☐ Chills/hair on arms stand up/ shivering
- ☐ Muscle ache/back ache
- ☐ Dilated pupils
- ☐ Irritability/anxiety
- ☐ Trouble sleeping
- ☐ Nausea
- ☐ Vomiting
- ☐ Loss of appetite
- ☐ Diarrhea
- ☐ Stomach cramps
- ☐ Increased blood pressure, respiration or heart rate

Verbatim response

10. Please name five types of other medicines that you should use caution with while taking morphine sulfate? [Score first five responses]

- ☐ Sleeping pills
- ☐ Pain medicines
- ☐ Anti-nausea medicines
- ☐ Tranquilizers
- ☐ Muscle relaxants
- ☐ Antihistamines
- ☐ Anti-anxiety medications
- ☐ Anti-depressants
- ☐ Cimetidine/tagamet
- ☐ Anticholinergic medications

Verbatim response

11. What does it mean for your body to be "opioid tolerant"?

- ☐ Correct (Your body is used to the medication)
- ☐ Incorrect
- ☐ Refused

Verbatim response

Appendix D (continued)

SURVEY INSTRUMENT

12. If you are taking morphine sulfate, you should call your doctor right away if you have any of what three symptoms?

- ☐ *Slow breathing*
☐ *Shallow breathing*
☐ *Faintness/dizziness/confusion*
☐ *Any other unusual symptom*

Verbatim response

13. What are five of the most common side effects of morphine sulfate?

- ☐ *Constipation*
☐ *Nausea*
☐ *Sleepiness*
☐ *Lightheadedness*
☐ *Dizziness*
☐ *Drowsiness*
☐ *Vomiting*
☐ *Sweating*

Verbatim response

14. True or False: If you forget to take your morphine sulfate, and are experiencing pain, you can take your usual dose when you remember.

- ☐ *True (correct)*
☐ *False*
☐ *Refused*

Verbatim response

15. Should you keep morphine sulfate oral solution in the refrigerator?

- ☐ *Correct (No)*
☐ *Incorrect*
☐ *Refused*

Verbatim response

Open Ended

16. According to this guide what is the most important thing you should know about Morphine Sulfate Oral Solution?

Appendix D (continued)

SURVEY INSTRUMENT

17. [Record time to completion]

Prior Use

18. Are you currently taking Morphine Sulfate?

- ☐ Yes
☐ No
☐ Refused

19. Have you ever taken Morphine Sulfate before?

- ☐ Yes
☐ No
☐ Refused

20. Has a family member taken this medication before?

- ☐ Yes
☐ No
☐ Refused

21. Did you help them take it?

- ☐ Yes
☐ No

Appendix D (continued)

SURVEY INSTRUMENT

Aranesp Questions

I am going to give you a Medication Guide with information about a prescription medication. Then I will ask you questions about that medication. You can look at the materials at any point during the interview. But to begin, please take some time to look over the information, and I'll begin the questions in a couple of minutes.

[START RECORDING TIME]

1. What condition does Aranesp help treat?

- ☐ *Correct (Anemia/low red blood cell count)*
- ☐ *Incorrect*
- ☐ *Refused*

Verbatim response

2. If you develop antibodies to Aranesp, what four symptoms are you most likely to have?

- ☐ *Tiredness*
- ☐ *Lack of energy*
- ☐ *Dizziness*
- ☐ *Fainting*

Verbatim Response

3. You should not take Aranesp under what four conditions?

- ☐ *If you have cancer and you are not receiving chemotherapy that may cause anemia*
- ☐ *If your cancer has a high chance of being cured*
- ☐ *Have cancer but have not signed the acknowledgement of counseling form/been counseled about the risks*
- ☐ *Uncontrolled high blood pressure*
- ☐ *Have ever had Pure Red Cell Aplasia*
- ☐ *Are allergic to any ingredients in Aranesp*

Verbatim Response

Appendix D (continued)

SURVEY INSTRUMENT

4. Name five symptoms of blood clots. [Score first five responses]

- ☐ Chest Pain
- ☐ Trouble breathing/shortness of breath
- ☐ Pain in legs
- ☐ Cool/pale arm or leg
- ☐ Confusion/speech problems
- ☐ Numbness/weakness
- ☐ Trouble Seeing
- ☐ Trouble walking/dizziness/loss of balance/coordination
- ☐ Fainting
- ☐ Hemodialysis vascular access problems

Verbatim Response

5. How is a dose of Aranesp given?

- ☐ Correct (Shot/injection)
- ☐ Incorrect
- ☐ Refused

Verbatim Response

6. What are the three most COMMON side effects of Aranesp?

- ☐ Swelling
- ☐ Rash
- ☐ Pain at injection site

Verbatim Response

7. Before starting Aranesp what other five health conditions should patients tell their doctor about?

- ☐ Heart Disease
- ☐ High Blood Pressure
- ☐ Seizure /Stroke
- ☐ Pregnant/Planning
- ☐ Breast feeding/Planning

Verbatim Response

Appendix D (continued)

SURVEY INSTRUMENT

8. Why is Aranesp given in the smallest dose possible?
- ☐ Correct (So hemoglobin doesn't get too high/ to prevent heart problems/death/lower chance of red blood cell tranfusion)
- ☐ Incorrect
- ☐ Refused

Verbatim Response

9. What are the seven main SERIOUS side effects of Aranesp?

- ☐ Heart problems
- ☐ Blood clots
- ☐ High blood pressure
- ☐ Seizures
- ☐ Antibodies
- ☐ Allergic Reactions
- ☐ Increased tumor growth

Verbatim Response

10. Aranesp helps you make more what?

- ☐ Correct (Red blood cells)
- ☐ Incorrect
- ☐ Refused

Verbatim response

11. True or False: You can take Aranesp if you have controlled hypertension.

- ☐ True (correct)
- ☐ False
- ☐ Refused

Verbatim Response

12. What should you do if you accidentally put Aranesp in the freezer instead of the refrigerator?

- ☐ Correct (Do not use it/throw away)
- ☐ Incorrect
- ☐ Refused

Verbatim Response

Appendix D (continued)

SURVEY INSTRUMENT

Open Ended

13. According to this guide, what is the most important thing you should know about Aranesp?

14. [Record time to completion]

Prior Use

15. Are you currently taking Aranesp?

- ☐ Yes
☐ No
☐ Refused

16. Have you ever taken Aranesp before?

- ☐ Yes
☐ No
☐ Refused

17. Has a family member taken this medication before?

- ☐ Yes
☐ No
☐ Refused

18. Did you help them take it?

- ☐ Yes
☐ No

Appendix D (continued)

SURVEY INSTRUMENT

Background

This last set of questions is about your background and personal characteristics. Some are health related and some are not, but it's important that you answer all of them.

I am going to read a list of medical conditions. I want you to tell me if a doctor or nurse has ever told you that you had any of these conditions.

	Yes	No	Don't Know
Heart attack	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
A stroke	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Heart failure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Enlarged heart	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Diabetes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fluid in the lungs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chronic bronchitis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Coronary heart disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Heart bypass surgery or angioplasty	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Asthma	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Emphysema	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

During the past 12 months, have you had any of the following:

	Yes	No	Don't know
Stroke	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Peripheral artery disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
High blood pressure or hypertension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
High cholesterol or hyperlipidemia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Angina	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Arthritis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cancer (if yes, specify)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please specify

Depression	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cataracts	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Deafness in one or both ears	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Any trouble hearing with one or both ears	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hip fracture	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Appendix D (continued)

SURVEY INSTRUMENT

In general would you say your health is...(INTERVIEWER: Read categories below)

- ☐ Excellent
- ☐ Very Good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Refused

(INTERVIEWER: Record Sex. Don't read categories)

- ☐ Male
- ☐ Female

What is the highest grade or year of school you completed? [DON'T READ CATEGORIES]

- ☐ 8th grade or less (elementary)
- ☐ Grades 9 through 11 (some high school)
- ☐ Grade 12 or GED (high school graduate)
- ☐ College 1 year to 3 years (some college or technical school)
- ☐ College 4 years or more (college graduate)
- ☐ Don't Know
- ☐ Refused

What race do you consider yourself? [DON'T READ CATEGORIES]

- ☐ Black or African American
- ☐ White or Caucasian
- ☐ Hispanic or Latino
- ☐ Asian
- ☐ Other (please specify)
- ☐ Don't Know
- ☐ Refused

If other, please specify

Appendix D (continued)

SURVEY INSTRUMENT

Now, I would like to ask you about your income. I know this is a sensitive topic, but it is important because your income affects your health and how you use medical care. Please tell me now how much money you earned last year. We need your total household income, but not the exact amount. I am going to show you a card with income categories on it and ask you to pick the category that is the closest to your total income.

(INTERVIEWER: Hand the participant the Income Scale)

What was your total household income in the past 12 months? Just give me the number from the right hand column on the card. *[READ NUMBER ONLY IF IT APPEARS THEY CANNOT READ]* *(INTERVIEWER: If patient reports income by month, then multiply by 12)*

- ☐ (1) Less than \$10,000
- ☐ (2) Between \$10,000 and \$14,999
- ☐ (3) Between \$15,000 and \$19,999
- ☐ (4) Between \$20,000 and \$24,999
- ☐ (5) Between \$25,000 and \$34,999
- ☐ (6) Between \$35,000 and \$50,000
- ☐ (7) Over \$50,000
- ☐ (777) Refused
- ☐ (999) Don't know

Including yourself, how many people are supported by this total household income?

Are you currently working for pay?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Refused

Appendix D (continued)**SURVEY INSTRUMENT**

Are you working part time or full time?

☐ *Part time*

☐ *Full time*

Appendix D (continued)

SURVEY INSTRUMENT

REALM

The last part of this interview will help us get an idea of how familiar people are with medical terminology. Please look at this list of words, beginning at the top of List 1. Say all of the words you know. If you come to a word you don't know, you can sound it out or just skip it and go on. Please read List 1, then List 2, then List 3 as best you can.

(INTERVIEWER: Check the words the participant pronounces incorrectly)

- | | | |
|-----------------------------------|---|---|
| <input type="checkbox"/> fat | <input type="checkbox"/> pelvic | <input type="checkbox"/> menstrual |
| <input type="checkbox"/> flu | <input type="checkbox"/> jaundice | <input type="checkbox"/> testicle |
| <input type="checkbox"/> pill | <input type="checkbox"/> infection | <input type="checkbox"/> colitis [kuh- <u>lahy</u> -tis, koh-] |
| <input type="checkbox"/> dose | <input type="checkbox"/> exercise | <input type="checkbox"/> emergency |
| <input type="checkbox"/> eye | <input type="checkbox"/> behavior | <input type="checkbox"/> medication |
| <input type="checkbox"/> stress | <input type="checkbox"/> prescription | <input type="checkbox"/> occupation |
| <input type="checkbox"/> smear | <input type="checkbox"/> notify | <input type="checkbox"/> sexually |
| <input type="checkbox"/> nerves | <input type="checkbox"/> gallbladder | <input type="checkbox"/> alcoholism |
| <input type="checkbox"/> germs | <input type="checkbox"/> calories | <input type="checkbox"/> irritation |
| <input type="checkbox"/> meals | <input type="checkbox"/> depression | <input type="checkbox"/> constipation |
| <input type="checkbox"/> disease | <input type="checkbox"/> miscarriage | <input type="checkbox"/> gonorrhea |
| <input type="checkbox"/> cancer | <input type="checkbox"/> pregnancy | <input type="checkbox"/> inflammatory |
| <input type="checkbox"/> caffeine | <input type="checkbox"/> arthritis | <input type="checkbox"/> diabetes [dahy-uh- <u>bee</u> -tis, -teez] |
| <input type="checkbox"/> attack | <input type="checkbox"/> nutrition | <input type="checkbox"/> hepatitis |
| <input type="checkbox"/> kidney | <input type="checkbox"/> menopause | <input type="checkbox"/> antibiotics |
| <input type="checkbox"/> hormones | <input type="checkbox"/> appendix | <input type="checkbox"/> diagnosis |
| <input type="checkbox"/> herpes | <input type="checkbox"/> abnormal | <input type="checkbox"/> potassium |
| <input type="checkbox"/> seizure | <input type="checkbox"/> syphilis | <input type="checkbox"/> anemia |
| <input type="checkbox"/> bowel | <input type="checkbox"/> hemorrhoids ([<u>hem</u> -uh-roid, <u>hem</u> -roid]) | <input type="checkbox"/> obesity |
| <input type="checkbox"/> asthma | <input type="checkbox"/> nausea [<u>naw</u> -zee-uh, -zhuh, -see-uh, -shuh] | <input type="checkbox"/> osteoporosis |
| <input type="checkbox"/> rectal | <input type="checkbox"/> directed | <input type="checkbox"/> impetigo [im-pi- <u>tahy</u> -goh] |
| <input type="checkbox"/> incest | <input type="checkbox"/> allergic | |
| <input type="checkbox"/> fatigue | | |

(INTERVIEWER: Special cases for REALM)

- | | | |
|---|--|--------------------------------------|
| <input type="radio"/> REFUSED to read ANY words | <input type="radio"/> COULD NOT read ANY words | <input type="radio"/> Forgot glasses |
| | | <input type="radio"/> ALL CORRECT |

Appendix D (continued)**SURVEY INSTRUMENT**

Thank you so much for participating in our study. We really appreciate you taking the time to speak with us. Thanks!

(INTERVIEWER: Select save responses, enter patient ID number, then submit and remember to rename text file in desktop folder)

Additional Comments on the Survey

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Appendix E

INSTITUTIONAL REVIEW BOARD APPROVAL NOTIFICATIONS FROM NORTHWESTERN UNIVERSITY AND THE UNIVERSITY OF ILLINOIS AT CHICAGO

Office for the
Protection
of Research Subjects

Northwestern University
750 North Lake Shore
Drive
Suite 700
Chicago, Illinois 60611

irb@northwestern.edu
Phone [312-503-9338](tel:312-503-9338)
Fax [312-503-0555](tel:312-503-0555)

6/10/2010

Dr. [Michael Wolf](#)

[General Internal Medicine Division](#)

676 N. Saint Clair Street FL2

Chicago IL 60611 USA

IRB Project Number: STU00025028

Meeting/Review Date: 6/10/2010

Review Type: Exempt

Protocol Sites:

Northwestern Medical Faculty Foundation (NMFF)

Other: (Specify and Explain) Chicago Lake Shore Medical Associates

Northwestern University (NU)

Sponsor Information:

SP0009305

Other Sponsor External Description: Abbott Laboratories Foundation

Other Sponsor Internal Description:

Investigator's Brochure:

There are no items to display

Appendix E (continued)

INSTITUTIONAL REVIEW BOARD APPROVAL NOTIFICATIONS FROM NORTHWESTERN UNIVERSITY AND THE UNIVERSITY OF ILLINOIS AT CHICAGO

Protocol Document:

[Human Subjects Protocol Version date 6-07-2010.doc](#)
[Approach Script Version 6-7-10.doc](#)
[Contact Card 6-7-10 for IRB.doc](#) (Please be sure to include the eIRB number on this card)

[verbal consent edited for initial submission 6-7-10.doc](#)

Protocol Title: Communicating Safe and Appropriate Drug Use to Patients & Families

Submission(s) Considered: New Project

Status: APPROVED

Your application for exemption for this human subjects research referenced above has been considered and approved. The claim of exemption is approved under 45 CFR 46.101(b) in accordance with the following criteria:

Category Type	Description
Category 2	Surveys, Tests, Interviews or Observations Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and ¹⁰⁰ any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Approval of this claim of exemption is granted with the understanding that any modification of the research that might affect the exemption status (Category listed above) must be submitted for review as a Revision. This approval does not cover Aims 2 and 3 of the Abbott grant, which are not eligible for exempt review. Please submit a new submission for those aims.

For more information regarding OPRS submissions and guidelines, please consult <http://www.northwestern.edu/research/OPRS/irb>.

This Institution has an approved Federalwide Assurance with the Department of Health and Human Services: FWA00001549.

Appendix E (continued)

**INSTITUTIONAL REVIEW BOARD APPROVAL NOTIFICATIONS
FROM NORTHWESTERN UNIVERSITY AND THE
UNIVERSITY OF ILLINOIS AT CHICAGO**

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

**Approval Notice
Initial Review (Response to Modifications)**

July 1, 2010

Bruce Lambert, PhD
Pharmacy Administration
241 P.H.A.R.M.
833 South Wood Street, M/C 871
Chicago, IL 60612
Phone: [phone number] / Fax: [phone number]

RE: Protocol # 2010-0469
“Communicating Safe and Appropriate Drug Use to Patients and Families”

Dear Dr. Lambert:

Your Initial Review (Response to Modifications) was reviewed and approved by the Expedited review process on June 22, 2010. You may now begin your research

Please note the following information about your approved research protocol:

<u>Protocol Approval Period:</u>	June 22, 2010 - June 21, 2011
<u>Approved Subject Enrollment #:</u>	250 at UIC
<u>Additional Determinations for Research Involving Minors:</u> These determinations have not been made for this study since it has not been approved for enrollment of minors.	
<u>Performance Sites:</u>	UIC, Northwestern University (lead site)
<u>Sponsor:</u>	Northwestern University
<u>PAF#:</u>	2010-02429
<u>Grant/Contract No:</u>	Not available
<u>Grant/Contract Title:</u>	Communicating Safe and Appropriate Drug
Use to Patients and Families	

Appendix E (continued)

**INSTITUTIONAL REVIEW BOARD APPROVAL NOTIFICATIONS
FROM NORTHWESTERN UNIVERSITY AND THE
UNIVERSITY OF ILLINOIS AT CHICAGO**

Research Protocol(s):

Communicating Safe and Appropriate Drug Use to Patients and Families, Version 2, 06/14/2010

Recruitment Material(s):

- a) Recruitment flyer, "How do you learn about medicines?" - Version 2.0, 06/14/2010

Informed Consent(s):

- a) A waiver of documentation (signed consent document) was granted under 45 CFR 46.117(c) to obtain verbal consent using a script and an Information Sheet
b) Information Sheet, Version 2.0, 06/14/2010
c) Script for verbal consent, Version 2, 06/14/2010

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific category:

(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
05/21/2010	Initial Review	Expedited	05/28/2010	Modifications Required
06/16/2010	Response To Modifications	Expedited	06/22/2010	Approved

Please remember to:

→ Use your **research protocol number** (2010-0469) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure, **"UIC Investigator Responsibilities, Protection of Human Research Subjects"**

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process. Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

Appendix E (continued)

**INSTITUTIONAL REVIEW BOARD APPROVAL NOTIFICATIONS
FROM NORTHWESTERN UNIVERSITY AND THE
UNIVERSITY OF ILLINOIS AT CHICAGO**

We wish you the best as you conduct your research. If you have any questions or need further assistance, please contact me at (312) 355-1609 or OPRS staff at (312) 996-1711. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Suzanne French, CCRP
IRB Coordinator, IRB # 3
Office for the Protection of Research

Subjects

Enclosure(s):

- 1. UIC Investigator Responsibilities, Protection of Human Research Subjects**
- 2. Informed Consent Document(s):**
 - a) Information Sheet, Version 2.0, 06/14/2010
 - b) Script for verbal consent, Version 2, 06/14/2010
- 3. Recruiting Material(s):**
 - a) Recruitment flyer, "How do you learn about medicines?" - Version 2.0, 06/14/2010

cc: Nicholas G. Popovich, Pharmacy Administration, M/C 871

VITA

NAME: James E. Duhig

EDUCATION: B.A., Speech Communication, University of Illinois at Urbana-Champaign, Urbana, Illinois, 2001

M.A., Communication, University of Illinois at Chicago, Chicago, Illinois, 2006

Ph.D., Pharmacy Administration, University of Illinois at Chicago, Chicago, Illinois, 2011

PROFESSIONAL EXPERIENCE: Manager, Regulatory Affairs Medical Devices and Human Factors, Abbott Laboratories, Abbott Park, Illinois, September 2011-present

Research Assistant, Abbott Laboratories Medication Guide Comprehension and Health Literacy Project, Abbott Park, Illinois, August 2010-August 2011

Research Assistant, University of Illinois at Chicago Tools for Optimizing Prescribing Monitoring and Education Center for Education and Research on Therapeutics, University of Illinois at Chicago, Chicago, Illinois, July 2008-December 2009

Teaching Assistant, Formulary Leveraged Improved Prescribing, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, Spring 2007-Spring 2010

Research Assistant, U.S. Attorney General Consumer and Prescriber Education Grant Program, University of Illinois at Chicago, Chicago, Illinois, June 2006-August 2010

Teaching Assistant, Drug Information and Statistics, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, Spring 2006

Teaching Assistant, Roles, Environments and Communication, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, Fall 2005

Research Assistant, Department of Pharmacy Administration, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, August 2005-August 2011

Manager, Procter & Gamble Pharmaceuticals, Chicago, Illinois, February 2002-August 2005

VITA (continued)

PROFESSIONAL MEMBERSHIPS:	<p>International Society for Pharmacoeconomics and Outcomes Researchers Member, 2006 to present</p> <p>UIC Student Chapter President, 2009</p> <p>UIC Student Chapter Treasurer, 2008</p>
HONORS:	<p>Outstanding Student Training Class 1 Award, Procter & Gamble Pharmaceuticals, 2002</p> <p>Outstanding Student Training Class 2 Award, Procter & Gamble Pharmaceuticals, 2002</p> <p>MVP of Chicago District, Procter & Gamble Pharmaceuticals, 2003</p> <p>van Doren Fellowship Recipient, UIC College of Pharmacy, 2008</p> <p>International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Distinguished Service Award, 2009</p> <p>Jesse Stewart Memorial Award, UIC College of Pharmacy, 2009</p>
PUBLICATION:	<p>Schiff GD, Galanter WL, Duhig J, Lodolce AE, Koronkowski MJ, Lambert BL. (2011) Principles of conservative prescribing. <i>Arch Intern Med.</i> 2011;171(16):1433-1440. doi:10.1001/archinternmed.2011.256</p>
CONFERENCE PRESENTATIONS:	<p>Schiff G, Duhig J, Edison M, Galanter W, Koronkowski M, Lambert BL, Lodolce A, Pickard AS, Wilke CT. DRUG Formulary Culture Survey: Measuring the Temperature of Clinicians' Boiling Blood. SGIM 32nd Annual Meeting, Miami Beach, FL, May 13-16, 2009.</p> <p>Duhig J, Edison M, Galanter W, Koronkowski M, Lambert BL, Lodolce A, Pickard AS, Wilke CT, Schiff G. Conceptual Issues in the Development of a Measure of Formulary Culture. ISPOR 14th Annual International Conference, Orlando, FL, May 16-20, 2009.</p>
INVITED PRESENTATIONS:	<p>"The Role of Physician Prescribing Data in Pharmaceutical Sales Rep Behavior." University of Illinois Communications Conference, Chicago, IL, March 10, 2006.</p> <p>"Neurontin Case History." UIC Department of Medical Education Seminar, University of Illinois at Chicago, Chicago, IL, September 26, 2007.</p> <p>"Use of Physician Prescribing Data." FLIP Symposium for Medical and Pharmacy Students. University of Illinois at Chicago, Chicago, IL, October 27, 2007.</p>

VITA (continued)

“Drug Rep Behavior and Physician Prescribing Data.” AMSA Student Lunch, Northwestern University, Chicago, IL. April 1, 2008.

“Pharmaceutical Advertising and Promotion.” Pritzker School of Medicine, University of Chicago, Chicago, IL, April 3, 2008.

“Pharmaceutical Advertising, Promotion and Physician Prescribing Data.” University of Illinois at Chicago Medical School, Resident Short-Courses, Chicago, IL. April 4, 2008.

“Evidence Based Medicine and the Pharmaceutical Industry: Pharmaceutical Advertising and Promotion.” Feinberg School of Medicine, Northwestern University, Chicago, IL, April 23, 2009.